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PYELOGRAPHIC CHANGES IN NECROTIZING RENAL PAPILLITIS

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Necrotizing papillitis has long been established as a definite entity and is not infrequently encountered in patients with diabetes mellitus; approximately five per cent of diabetic deaths have been attributed to this lesion (Pellegrin, King; Edmondson, Martin and Evans). The clinical and pathological picture of the disease, its etiology and pathogenesis have been widely considered in the last few years, but very little information is available on the pyelographic appearance of the lesion. This report is concerned with pyelographic changes in three patients with this disease.

The lesion is of urological importance because its pyelographic appearance is similar to that of renal tuberculosis (Harrison and Bailey) and the problem of differential diagnosis may arise from pyelography when the clinical etiology is not distinct. Papillary renal necrosis was first described by Von Friedreich in 1877 at autopsy, and the first pyelographic changes were reported by Gunther in 1937. It is known to occur most commonly in diabetics, 1.5 per cent of all deaths having been attributed by Pellegrin and Frederick to this complication of diabetes mellitus. Other etiological factors have been postulated, particularly obstructive uropathy (Edmondson, Martin and Evans; Wiesel and McManus; Tamaki and Whitman). Retrograde pyelograms (Eskelund), amyloid degeneration (Mellgran), and peri-arteritis nodosa also have been considered as causes. The other urological factor of significance is the fact that the lesion is not necessarily terminal, as healing has been observed at least twice (Edmondson, Martin and Evans; Wiesel and McManus). Prompt diagnosis and management of cause, i.e., diabetes, obstruction, etc., and of urinary tract infection are apparent as essential to the welfare of patients with this lesion. One such case of healing, the first to be reported by pyelographic demonstration, is included in this report (case 1).

The clinical picture is variable within certain limits, but in general has been one of marked upper urinary tract infection, tenderness in the costovertebral angle, sloughing of papilla with passage of tissue fragments, oliguria and later polyuria and nitrogen retention. It is important to maintain a degree of suspicion in likely candidates, so as to allow early clinical and pyelographic diagnosis which will promote early correction of causative agents and vigorous therapeutic regimens.

The pyelographic abnormalities have been described and usually follow the pattern that would be expected from destructive lesions of the renal papillae which are loss of calyceal architecture with deformity, irregularity and cavitation of the renal calyx. Any degree of such changes may occur as demonstrated in the three cases presented. Enlargement of the renal outline also was observed

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in each case, apparently due to parenchymal inflammatory reaction. In no case was there evidence of mechanical obstruction or stasis present. The differential diagnosis most often is from that of renal tuberculosis, but tumor of renal pelvis, chronic nonspecific pyelonephritis, actinomycosis or other ulcerative lesions may be considered.

Review of the literature reveals that over 100 cases of papillary necrosis have been reported and it is no longer considered a rare lesion, but only eight with definite pyelographic demonstration could be found. Most authors concur in the belief that antemortem diagnosis could be made more often if urographic studies were employed in likely candidates.

CASE REPORTS

Case 1. (E. H.) A 57 year old white woman, a known diabetic of 25 years' duration, was admitted to Barnes Hospital on August 15, 1950. On admission she was febrile, had a marked urinary tract infection and was near coma and shock of diabetic origin with FBS of 287 and nonprotein nitrogen of 64. Urine studies for tuberculosis, including culture and guinea pig injections were negative but positive for gram negative bacilli. Bilateral costovertebral angle tenderness, most marked on the right, was present. Seven days after admission a right retrograde pyelogram (fig. 1, *A*) showed massive cavitation of all calyces and enlargement of both renal shadows. The patient was treated with insulin and terramycin and clinically responded slowly. Bilateral retrograde pyelograms made on September 26, 1950 (fig. 1, *B*) revealed a marked change of the right upper urinary tract with blunted rounded calyces replacing the cavities, suggesting that a healing process had occurred. In the 5 week interval between pyelograms she received antibiotics and insulin, her insulin requirements having been raised from 16 units protamine zinc insulin pre-admission to 96 units pro-

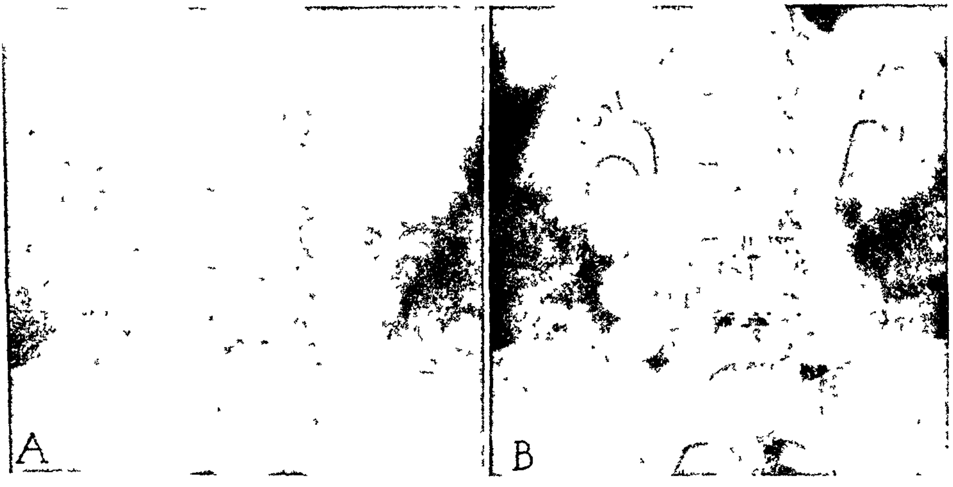

FIG. 1. Case 1. *A*. Right retrograde pyelogram before therapy. Destruction of all calyces with cavitation and enlarged renal shadows with normal renal pelvis are demonstrated. *B*, bilateral retrograde pyelograms 5 weeks later, after therapy for diabetes and urinary tract infection had been administered. Blunted, rounded calcyes with a decrease in size of renal shadow are apparent, suggesting that a healing process had occurred paralleling clinical improvement.

tamine zinc insulin per day. Other pyelograms made one to six months later showed no change and her clinical condition remained satisfactory.

Case 2. (I. P.) A 58 year old Negress, a known diabetic, was admitted to University Hospital in diabetic coma with an elevated nonprotein nitrogen. Retrograde pyelograms (fig. 2) revealed bilateral loss of normal calyceal architecture with cavitation of practically all calyces and enlarged renal shadows. Urine studies were negative for tuberculosis. Diabetes was controlled, antibiotics were administered and patient recovered clinically in 2 weeks. She was dismissed shortly thereafter and followup pyelograms could not be obtained.

Case 3. (M. C.) A 28 year old white woman was admitted to University Hospital on August 21, 1951, because of a complaint of right flank pain and suspected psychogenic disturbance. She had had four episodes of urinary tract infection prior to admission and was treated with sulfonamides, usually responding in three or four days. One week after admission she was found to have pyuria and both excretory and retrograde pyelograms showed no abnormalities except slight dilatation of the upper third of the right ureter. Her blood and urine sugar were normal, nonprotein nitrogen was normal and urine contained many pus cells and gram negative bacilli which were identified on culture as Proteus. Urine studies for AFB were negative. She improved slowly on sulfonamides and streptomycin and was discharged a week later. Within the next 3

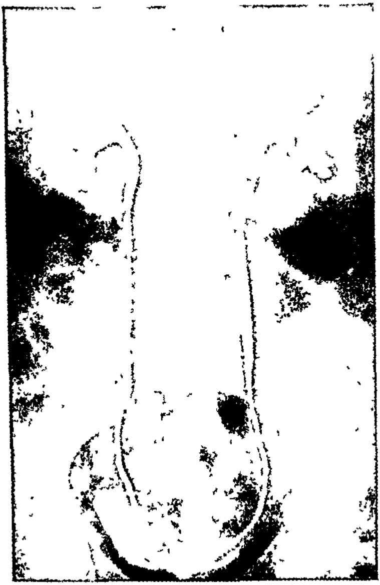

FIG. 2 Case 2. Bilateral retrograde pyelograms showing loss of normal calyceal architecture, multiple cavities and large renal outlines

months she had three recurrences of the urinary tract infection and was readmitted in February 1952, having shaking chills and temperature elevations to 104F, marked pain in the right costovertebral angle and tenderness, Proteus and Pyocyaneous in urine with slow response to chemotherapy. Another set of pyelograms revealed slightly more dilatation of upper third of the right ureter, so the right kidney was explored and no gross changes were evident. Nephrostomy was done and right ureter splinted. The patient had an uneventful course for 9 days when pain in the right costovertebral angle, chills and daily temperature spikes to 104–105F, b.d. recurred. Right nephrectomy was done as an emergency procedure on the twentieth postoperative day. Pathological report was necrotizing renal papillitis. Degenerative arteriolar lesions were present in both renal pelvis and parenchyma, but due to the presence of widespread pyelonephritis, it could not be determined whether these lesions were primary or secondary to the pyelonephritis. Nephrectomy relieved pain in the right flank but in about 8 days it recurred in the left costovertebral angle accompanied by chills, fever and pyuria. The nonprotein nitrogen then became elevated for the first time and a left retrograde pyelogram (fig. 3) revealed some calyceal deformity that suggested papillary necrosis rather than changes of pyelonephritis alone. Urine output steadily increased, specific gravity decreased and the nonprotein nitrogen rose to 106 mg. per cent, before decreasing. Pyuria has persisted in spite of use of all known antibacterials and the nonprotein nitrogen has apparently become stabilized at around 60 mg. per cent. She has improved somewhat clinically with moderate pain over the left costovertebral angle. On the assumption that peri-arteritis nodosa, secondary to prolonged therapy with sulfonamides, might be the etiological factor responsible, patient

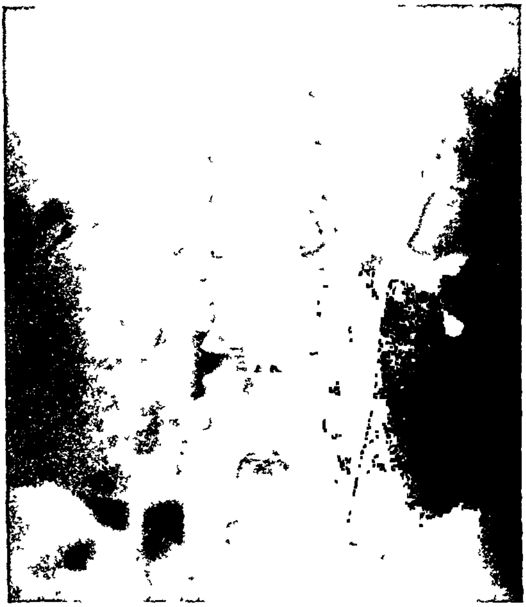

FIG. 3 Case 3. Left retrograde pyelogram showing calyceal deformity and enlargement of renal shadow. Right kidney had been removed 2 weeks previously and a pathological diagnosis of necrotizing renal papillitis was made.

was given ACTH but it had to be discontinued after 3 days because of side effects and no beneficial response in the remaining left kidney was observed

CONCLUSIONS

Characteristic pyelographic changes do occur in papillary necrosis of the kidney, which simulate renal tuberculosis and differ from the changes of chronic pyelonephritis

Three cases are reported with demonstrable pyelographic lesions, two of which occurred in diabetics and one in which the etiology was not clear Other cases showing pyelograms with changes ascribed to this lesion have been reported

In one case, pyelograms were made before and after healing of the lesion, the first such case reported

The role of peri-arteritis nodosa due to sulfonamide reaction as a pathogenic factor of the lesion is discussed and in one case considered to be the likely cause

Strict aseptic technique should be followed in instrumentation of diabetics in an attempt to introduce no new organisms, since diabetic urine usually is a fertile culture medium

Prompt recognition of this entity and its etiology which is usually diabetes is *essential* to institution of proper management

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PARTIAL NEPHRECTOMY

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Partial nephrectomy for localized renal disease is a well established operation. Stimulated by the absolute necessity of conserving renal tissue in some cases, and by the desirability of so doing in others, many workers have made contributions to the development of this procedure. While the indications for this operation are pretty well agreed upon, there is no general agreement as to the actual technique of its performance. The purpose of this article is primarily to call attention to the most satisfactory operative technique which the authors have encountered, and to present 6 cases in which this technique was used, as well as to discuss the indications briefly.

The first partial nephrectomies were performed in the latter nineteenth century by such men as Czerny, Tuffier, and Tillman. Tuffier in 1891 was the first to use catgut sutures, a great improvement over simply packing the wound as had been done previously. Many of the early attempts at partial nephrectomy were complicated by primary and secondary hemorrhage and urinary fistulas. These complications combined with unfavorable results in poorly selected cases, particularly in those of tuberculosis and malignant tumors, caused the operation to fall into disuse. However in the early twentieth century active interest in partial nephrectomy revived with improvements in surgical technique and anesthesia, so that it has now become the operation of choice in certain selected cases.

The cases in which partial nephrectomy has become the operation of choice are those where the pathological process is limited to one area of the kidney, and in which resection of that area will not jeopardize the integrity of the remaining portion of the kidney. This operation is often indicated in the treatment of calculus disease, of hydrocalyx with or without stone, and more recently in the surgical therapy of tuberculosis localized to one part of the kidney. It has been used in the treatment of benign tumors, renal carbuncle, cortical abscess, renal infarction, simple cysts, echinococcus cysts and renal fistulas. It is often indicated in the treatment of hydronephrosis, pyonephrosis, ureteral ectopia or benign neoplasm when these occur in one half of a kidney with reduplicated pelves and ureters, and when the other half is normal. Finally partial nephrectomy may necessarily have to be used in the treatment of a malignant tumor in a solitary kidney.

The use of partial nephrectomy in renal lithiasis is of particular importance. It has been frequently observed that calculi often arise originally and later recur in the same area of a given kidney. The reason for this is that calculi, especially if in poorly draining calyces, may give rise to chronic localized infection and

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erosion of epithelium with subsequent encrustation with lime salts which act as foci for recurrent calculi, so-called stone-bearing area. This situation has recently been reviewed by Steward, who points out that pyelolithotomy and nephrolithotomy do not always remove the focus, and that calculi recur in 15 to 30 per cent of reported series of cases. He believes that these recurrent calculi usually arise from the same calyceal nest and that removal of this area will reduce the incidence of recurrent calculi. In some cases, using very careful radiographic technique, he was able to demonstrate minute calcific deposits in the affected calyx or adjacent pyramid as the probable source of recurrent calculi. Steward's theory is substantiated by the fact that the recurrence rate of calculi in his series of 101 personal cases in which he removed the stone-bearing area by performing partial nephrectomy was only 6.8 per cent. These cases were done over a period of thirteen years, and no case was followed for less than two years. In view of these findings, it is apparent that the operation should be used more widely in the treatment of renal lithiasis.

Partial nephrectomy is now often indicated in the treatment of renal tuberculosis with cavitation localized to one portion of the kidney. Prior to the advent of streptomycin, para-aminosalicylic acid, and isoniazid (iso-nicotinic acid hydrazide), tuberculosis constituted a contra-indication to this procedure. However at the present time, in suitable cases, after preparation of the patient with these drugs, the procedure is quite successful. Semb and Lattimer have each reported a series of cases of partial nephrectomy for localized renal tuberculosis with favorable results.

TECHNIQUE

In order to control the profuse bleeding from the renal parenchyma during the operation of partial nephrectomy, various means of temporarily occluding the vessels of the renal vascular pedicle are employed, such as rubber-shod clamps, tourniquets of rubber or gauze, and finger compression. Unlike the authors, as will be explained presently, most operators perform sharp knife excision of the diseased segment by a wedge resection, with closure of the resulting defect by mattress sutures, or by the cobbler stitch of Tuffier. A satisfactory degree of hemostasis is usually achieved by suture ligature of the larger vessels bleeding from the cut surface, supplemented by pieces of muscle or fat applied to that surface. However Herbst and Polkey have shown that deep sutures for hemostasis and for closure cause necrosis of a large amount of renal substance, which is a definite drawback to this technique when it is important to conserve as much renal tissue as possible. Diathermy has been used by some for hemostasis, but is generally condemned as giving rise to too much necrosis and to the danger of secondary hemorrhage.

Lattimer, using partial nephrectomy for localized renal tuberculosis, has described a technique in which the vessels in the renal parenchyma are clamped and ligated as they are encountered during the resection, and hemostasis is thus obtained by accurate surgical technique. The infundibulum or calyx is divided and then closed carefully with suture.

In the cases reported below, the following technique, similar to that reported by Lattimer, was used. Excellent exposure is needed, which often makes resection of the twelfth rib advisable. The kidney, enclosed in Gerota's fascia and perinephric fat, is freed posteriorly from the quadratus lumborum and iliopsoas muscles to the region of the renal pelvis and pedicle. At this point Gerota's fascia is incised horizontally and, with the perinephric fat, is reflected anteriorly and medially from the kidney in a single sheath, being left attached near the pelvis on the anterior aspect of the kidney. The renal capsule can be conserved by sharp dissection of the perinephric fat from the kidney, as blunt dissection may fragment and thin the capsule, making it impossible to use it later in the closure of the renal wound. The renal vessels are then isolated, and a small light Serrafine-Diffenbachs ("bulldog") blood vessel clamp or rubber-shod light intestinal clamp is placed on the artery. A circumferential incision is then made through the capsule which is stripped back from the kidney to a point proximal to the proposed line of resection. See figure 1. Then, using the handle of the knife, the renal sub-

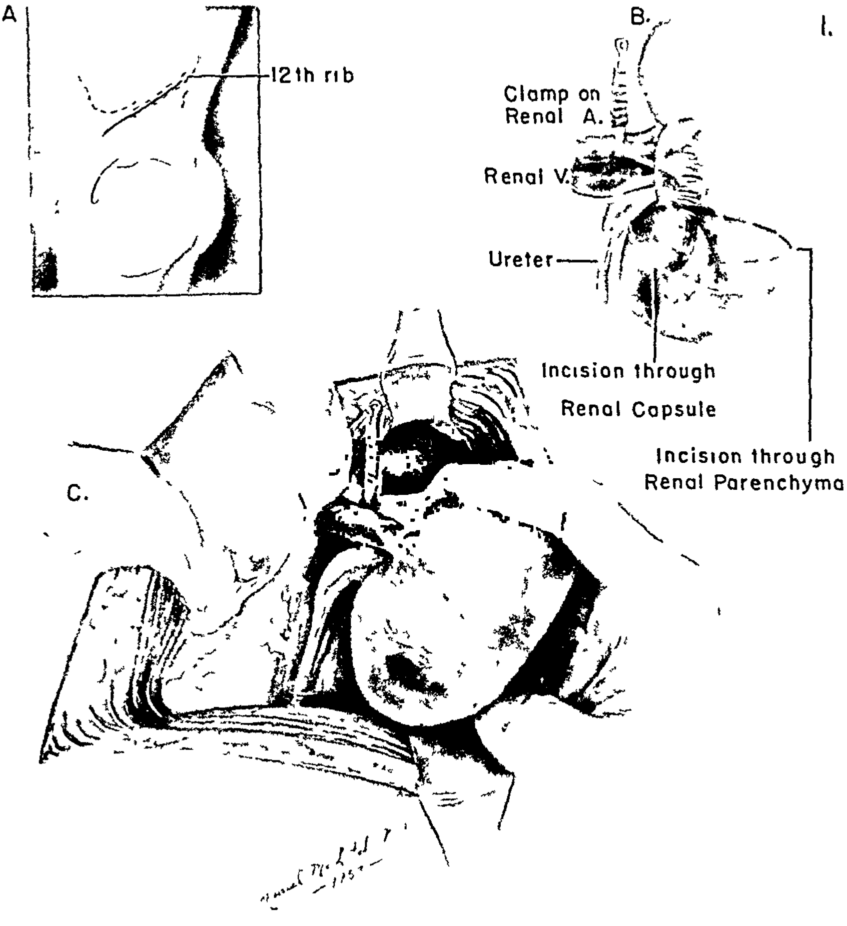
A
12th rib
B.
1.
Clamp on Renal A.
Renal V.
Ureter
Incision through Renal Capsule
Incision through Renal Parenchyma
C.

FIG. 1 *A*, site of incision (resection of twelfth rib). *B* and *C*, exposure of kidney. Bull dog clamp applied to renal artery. Sites of incisions through renal capsule and through parenchyma are indicated by lines.

stance is separated by blunt dissection Because the vessels are more resistant than the soft renal parenchyma, they stand out as the dissection progresses and are easily seen, clamped, and ligated The dissection is continued, until the infundibulum of the calyx being removed is exposed See figure 2 The infundibulum is severed leaving a small portion above the line of resection to facilitate an accurate water-tight closure with a continuous 4-O chromic catgut intestinal suture

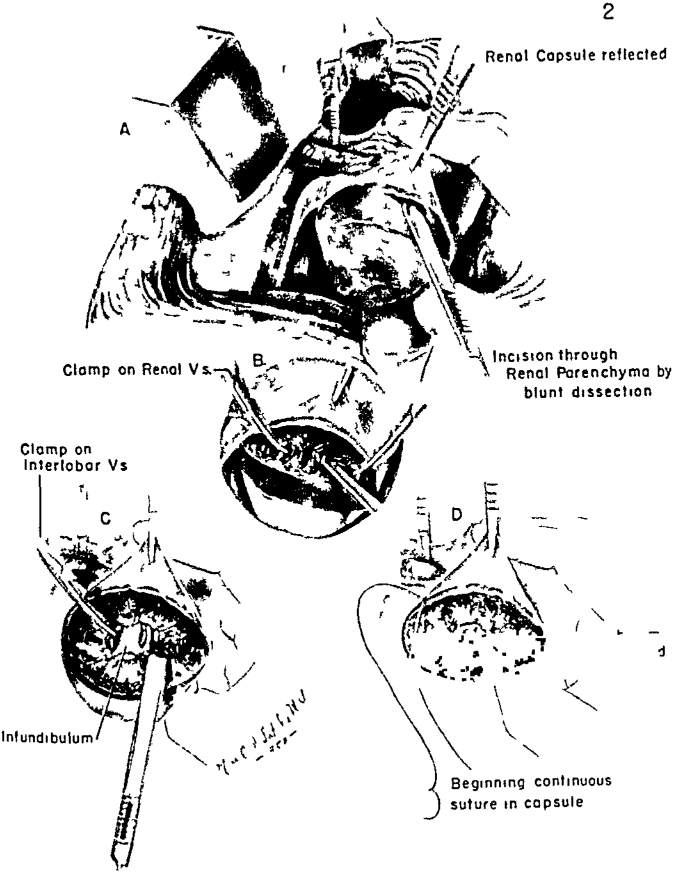
2
Renal Capsule reflected
A
Incision through Renal Parenchyma by blunt dissection
Clamp on Renal Vs.
B
Clamp on Interlobar Vs
C
D
d
Infundibulum
Beginning continuous suture in capsule

Fig 2 *A* blunt dissection through parenchyma *B*, small vessels in parenchyma are clamped as dissection progresses *C*, small vessels have been ligated Infundibulum exposed and about to be divided *D*, infundibulum sutured

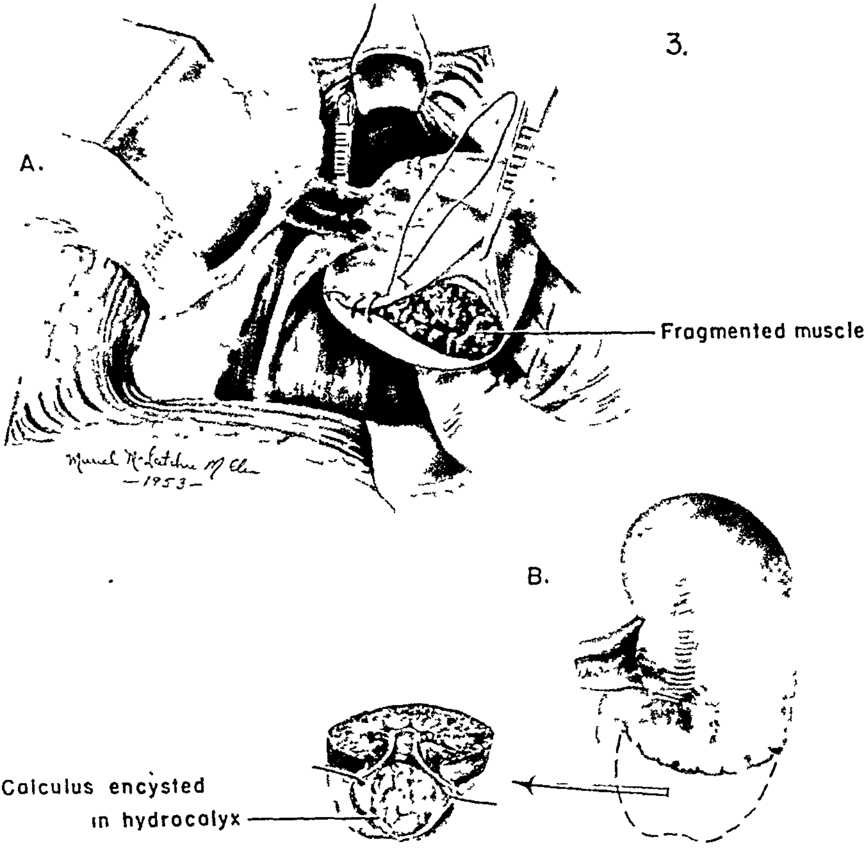

FIG 3. *A*, suture of capsule over cut surface of kidney. *B*, resected portion of kidney containing stone in hydrocalyx.

On removing the clamp from the artery, hemostasis may be adequate or may need to be supplemented by small stitch ligatures. A small amount of fragmented muscle or a piece of fat or Gelfoam is then placed on the cut surface of the kidney and the capsule is closed over this with a continuous 0000 chromic catgut intestinal suture. See figure 3. The sheath of Gerota's fascia and perinephric fat is then replaced over the kidney and held in position with a few sutures. The wound is closed with drainage.

The renal artery may be safely occluded for the 15 to 20 minutes necessary to accomplish the operation. Shorter time limits have been quoted, but Linton, in performing splenorenal vein anastomosis, has occluded the renal artery for as long as 45 minutes without adverse effect on the kidney. Priestley has also occluded renal vessels for a similar time in removing branched renal calculi.

CASE REPORTS

Case 1. B.C., R No. 9667. A 40-year-old mail clerk was admitted to the Boston VA Hospital with hematuria, right flank pain, and intermittent chills and fever

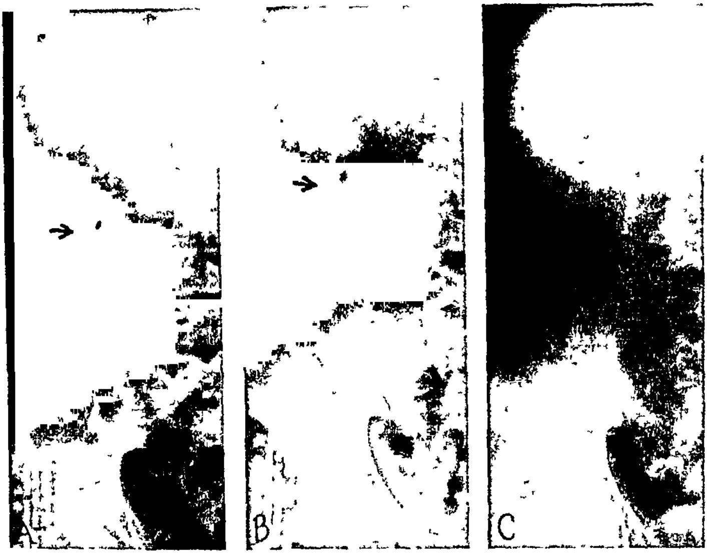

FIG. 4. Case 1. *A*, note two recurrent calculi in lower calyx of kidney. *B*, excretory urogram also showing recurrent calculi. *C*, excretory urogram 6 weeks after resection of lower pole of kidney containing calculi showing excellent function.

of 1 month's duration. Four years prior to admission he had been hospitalized for similar complaints and a staghorn calculus had been removed by splitting the right kidney. He had been well since that time until the onset of the present illness. Excretory urograms revealed two calculi 1 cm. in diameter in the right lower calyx. Partial nephrectomy was performed and recovery was uneventful. An excretory urogram 6 weeks postoperatively revealed good function in the remaining portion of the kidney (fig. 4).

Case 2. D. B., R No. 10754. A 65-year-old elevator operator was admitted to the Boston VA Hospital because of a right upper quadrant mass. One year previously a left nephrectomy had been performed for a tumor (papillary cystadenocarcinoma). Physical examination revealed a round tennis ball-sized, hard, nontender mass in the right upper quadrant which moved with the kidney on respiration. An excretory urogram revealed a round soft tissue mass overlying the renal shadow. There was no change in the contour of the renal pelvis, calyces, or ureter. At operation a 10 cm. tense whitish-yellow tumor mass presented, attached by a narrow base to the anterior lip of the renal sinus. A small wedge of renal tissue containing the attachment of the tumor was removed. The bleeding was controlled with a few interrupted sutures, and no closure of the renal defect was necessary. The pathologist reported the tumor as papillary cystadenoma. Recovery was uneventful. An excretory urogram 8 months postoperatively revealed good function in the remaining portion of the kidney.

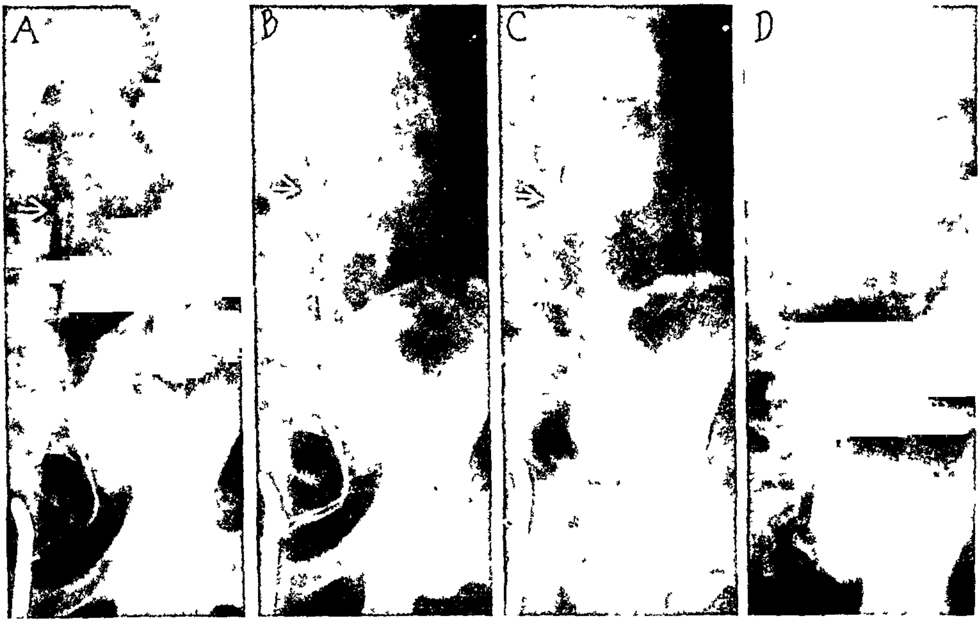

FIG. 5. Case 3. *A*, note complete reduplication of ureters and pelves and calculus obstructing upper left ureter. *B* and *C*, retrograde pyelograms showing normal lower half of reduplicated left kidney, but advanced hydronephrosis of upper half and hydro-ureter secondary to obstructing calculus. *D*, excretory urogram 4 months after heminephrectomy showing normal remaining lower half of kidney.

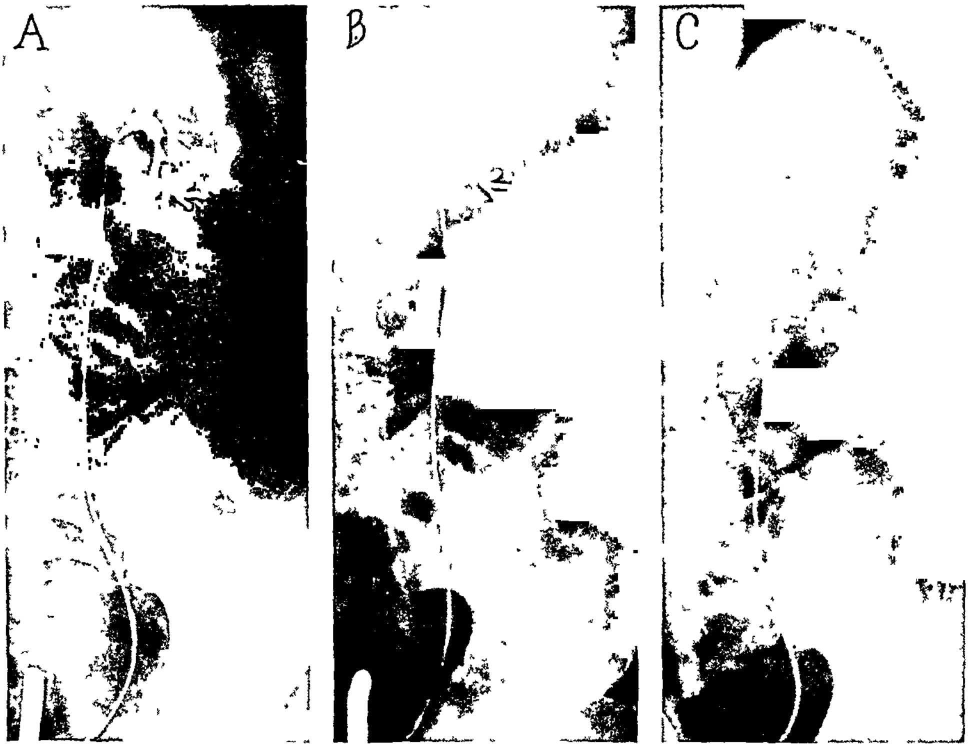

FIG 6. Case 4. *A* and *B*, retrograde pyelograms, anteroposterior, *A*, and oblique, *B*, views showing tuberculous cavities off the lowest calyx. *C*, retrograde pyelogram of same kidney 5 months after resection of lower pole containing tuberculous cavities. Urine now free of tubercle bacilli and excretory urogram (not shown) reveals normal function of kidney.

Case 3. J.C., R No. 6607. A 39-year-old mason was admitted to the Boston VA Hospital with left flank pain, chills, fever, and hematuria. Several similar previous attacks had been relieved after passing a stone. The urine was loaded with pus cells. Cystoscopy revealed four ureteral orifices, and retrograde pyelograms revealed complete bilateral reduplication of the ureters and renal pelves. The two lower components were normal. The right upper pelvis contained a small calculus. The left upper pelvis revealed advanced hydronephrosis secondary to a calculus in the ureter just below the ureteropelvic junction. At operation the two left ureters were found closely adherent to each other. The affected upper ureter was dissected free and divided below the stone, and then the upper half of the left kidney was removed in the manner described. Recovery was uneventful. An excretory urogram 4 months postoperatively revealed good function in the remaining portion of the kidney (fig. 5).

Case 4. E.F., R No. 9826. A 41-year-old maintenance supervisor had been admitted to another hospital 6 months previously with a chief complaint of total painless hematuria of 3 days' duration. Retrograde pyelography at that time revealed multiple small cavities branching from the lower group of calyces of the right kidney, and tubercle bacilli were cultured from the urine from that kidney. The patient was placed on streptomycin 1 gm. every 3 days, and 200 mg. isoniazid (isonicotinic acid hydrazide) and 12 gm. para-aminosalicylic acid daily. He was continued on this regimen for approximately six months. Repeat right retrograde

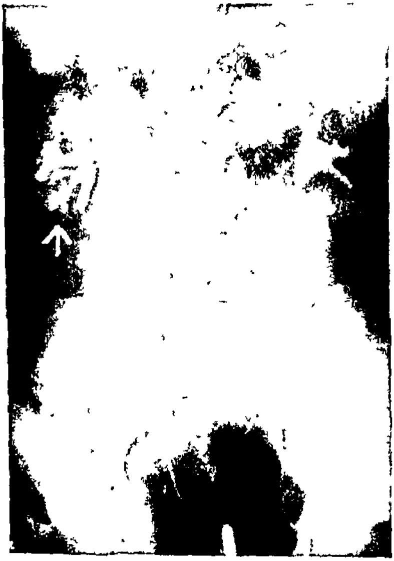

FIG. 7 Case 5 Retrograde pyelogram 11 months after removal of calculus at ureteropelvic junction and resection of lower pole of kidney containing numerous small calculi. No recurrence of calculi; good function demonstrated by excretory urography (not shown)

pyelograms revealed that the previously seen cavitation in the lower pole of the kidney was considerably smaller but still present. He was referred to the Boston VA Hospital where partial nephrectomy was done. It is now 5 months after operation, and the aforementioned antibiotic therapy will be continued for a total of 6 months. Repeated cultural studies have been negative. Excretory urograms 5 months postoperatively revealed good function in the remaining portion of the kidney (fig. 6).

Case 5. J.G., R No. 9833. A 38-year-old mail clerk was admitted with a chief complaint of severe, colicky right loin pain, and chills and fever of 48 hours' duration. The patient had been previously treated for right ureteral calculi, and was known to have a group of calculi in a dilated right lower calyx. He had been asymptomatic for 6 years. The patient's temperature was 103F; he was dehydrated and was found to have marked tenderness in the right costovertebral angle. Excretory urograms revealed a 2 cm. calculus at the right ureteropelvic junction and many smaller calculi in the right lower calyx. After proper preoperative preparation, a right pyelolithotomy and resection of the lower pole of the kidney were done in the manner described. Recovery was uneventful. Excretory urograms 11 months postoperatively revealed good function in the remaining portion of the kidney, and no recurrence of calculi (fig. 7).

Case 6. C.S., R No. 10247. A 44-year-old laborer was admitted with bilateral

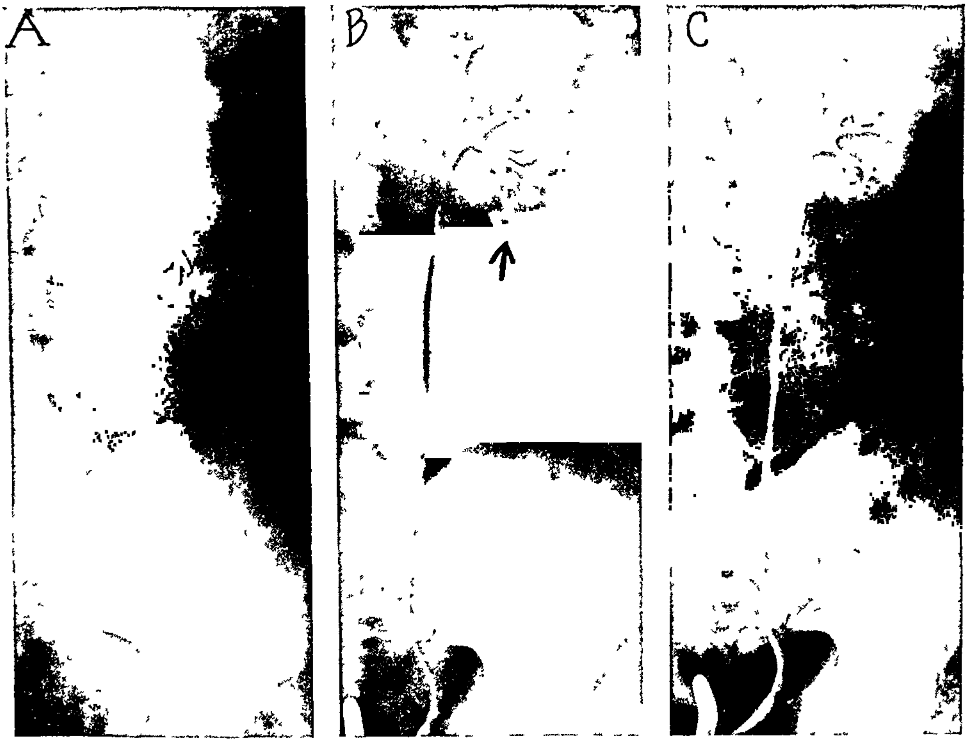

FIG. 8. Case 6. *A* and *B*, plain film and retrograde pyelogram showing several calculi in lower pole of kidney. Infection present. *C*, retrograde pyelogram 3 months after resection of lower pole of kidney. Excretory urography (not shown) indicated good function No recurrence of calculi; cure of infection.

flank pain of 7 to 8 years' duration. X-ray studies revealed no opaque calculi on the right, but did reveal several calculi in a dilated left lower calyx. Retrograde studies and urine examination revealed infection in the left kidney. A left partial nephrectomy was done with uneventful recovery, and with cure of infection, and relief of symptoms on that side. Excretory urograms 3 months postoperative revealed no recurrence of calculi and good function in the remaining portion of the kidney (fig. 8).

SUMMARY

The indications for partial nephrectomy are discussed briefly, emphasizing its value in renal lithiasis and tuberculosis

A comparatively new operative technique for partial nephrectomy, which has been used by the authors with great satisfaction, is reported upon.

The features of this technique are:

A) Resection by blunt dissection, thus enabling individual blood vessels to be seen, clamped, and ligated individually.

B) Accurate water-tight closure of infundibula or calyces transected.

C) Closure of the capsule, containing some muscle, fat or Gelfoam, over the wound of excision.

D) Preservation of Gerota's fascia and the perinephric fat in one sheath-like piece, which is replaced to cover the kidney at the end of the operation.

The advantages of this technique over the commonly used sharp knife wedge resection are:

A) More accurate and better hemostasis.

B) Less destruction of renal tissue, since it is not necessary to use mattress sutures for hemostasis or closure

Six cases, in which this technique was used, are reported. The postoperative follow-up results have been excellent.

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THE CLINICAL USE OF TERMINAL ILEUM AS A SUBSTITUTE URETER

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The urologic surgeon, ever concerned with conservation of the nephron, is often confronted with the problem of extensive loss of effective ureteral continuity. Trauma, chronic inflammation, neoplasm, radiation, and primary neuromuscular disorders comprise an etiologic list which demands no further elaboration. The surgeon who elects to sacrifice a potentially normal kidney by reason of seemingly irreparable ureteral disease does so not without misgivings, especially in those entities prone to future involvement of the contralateral side. It is true that nephrectomy or nephro-ureterectomy is often a necessity by reason of the nature of the primary entity, or in the interest of the patient may be preferable to such alternatives as cutaneous ureterostomy or nephrostomy, if the opposite kidney is normal. The concept of renal salvage, however, does not condone nephrectomy in instances of ureteral damage where circumstances permit the utilization of techniques designed to circumvent the loss. To this end, reimplantation of the ureter into the bladder, reconstruction of ureter from a tube of bladder wall and uretero-ureteral anastomosis have been effectively employed.

There are those instances, however, where the techniques mentioned are unsuitable by reason of the extent, location, or bilaterality of the process. This has led investigators to search elsewhere for a suitable substitute. It is understandable that, of the many structures considered, the small intestine, especially the ileum, has ranked high on the list. Its similarity to the ureter as a muscular structure possessed of effective peristaltic activity, its rich blood supply, its mobility, and its availability without loss of gastro-intestinal continuity has made it, at least mechanically, an ideal choice. Physiologically, however, one of its major mucosal functions, that of absorption, has rendered it unsuitable, at least in the opinion of early investigators, as a conveyor of urine. Steinke, Baird, Scott and Spencer, Hinman and Belt, and Bollman and Mann in separate investigations carried out from 1909 through 1927 demonstrated the inadvisability of transplantation of the ureters into an intact small intestine. In most instances the rapid death of laboratory animals subjected to such a procedure was attributed to absorption of urinary constituents.

Recent investigators, such as Matsumoto and Mersheimer, reported successful use of isolated segments of small bowel for transport of urine in dogs. They used short segments of ileum one end of which was exteriorized. Matsumoto noted a rise in nonprotein nitrogen in his animals the first week after operation with subsequent fall to normal. McLean and Fais were successful in ac-

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complishing almost complete substitution of one or both ureters in dogs and maintained continuity by an ileovesical anastomosis. They, too, noted transient elevations in nonprotein nitrogen with return to normal in the immediate postoperative period. In addition they made determinations of plasma chloride and carbon dioxide combining power and failed to note significant postoperative alterations Davids and Lesnick reported similar results in nine dogs as has Bitker in the same laboratory animal.

Encouraged by this modification of the original concept of the physiologic unsuitability of small intestine for urinary transport, surgeons have again revived attempts to utilize small bowel for this purpose. Bricker and Eiseman have made satisfactory use of short segments as a substitute bladder. Cibert and Couvelaire have independently reported the clinical use of ileum as a substitute ureter. Foret and Heusghem recently employed an ingenious U-shaped loop of small bowel for bilateral substitution. Single cases have also been reported by Rack and by Ortved. The present report deals with the detailed findings in four additional cases studied at the University of Michigan.

CASE REPORTS

Case 1. L. A., 721001, a 6-year-old girl was admitted to University Hospital on March 19, 1952 with a past history of recurrent urinary tract infection. She was found on pyelography to have bilateral hydro-ureter with narrowing of the ureter near the ureterovesical junction. A cystogram showed no reflux (fig. 1). Retrograde ureteral catheterization was accomplished without difficulty with a No 5 ureteral catheter. Renal function studies showed mild impairment. On March 31, the patient was operated upon and re-implantation of the ureter

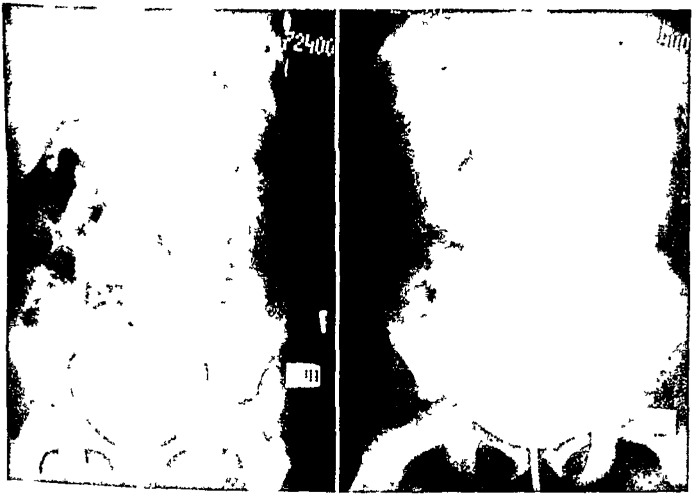


FIG. 1

carried out on the left, bypassing the area of narrowing found just above the bladder level. At the time of operation the ureter appeared adynamic, was dilated, thin-walled and tortuous. The patient made an uneventful recovery but in the next four months continued to have recurrent urinary tract infection associated with sepsis and left flank pain. Cystogram now demonstrated reflux on the operated side; excretory urogram showed no change in the previously noted hydro-ureter (fig. 2). It was felt that substitution of a more active peristaltic structure for the diseased left ureter might offer a reasonable solution to her problem.

On August 11, a curved left lower abdominal incision was made and the peritoneal cavity opened. A 32 cm. segment of terminal ileum was selected and found to lie comfortably in the left gutter, and would on tenting from two points extend from the left kidney hilus to the bladder in a relaxed fashion. The mesentery of this section of bowel was incised and the communicating vessels ligated and sectioned. The bowel was then divided between crushing clamps at its distal and proximal ends. An end-to-end anastomosis of the remaining bowel was accomplished in the usual fashion with two layers of interrupted silk to re-establish gastro-intestinal continuity. At this point the descending colon was freed from its bed in the left gutter and the left kidney mobilized, and the entire ureter and lower one-third of the renal pelvis excised. A nephrostomy was then performed. This accomplished, the isolated segment of ileum was then brought over the top of the descending colon and the upper end united to the renal pelvis in an end to end fashion, using interrupted sutures. A 3 cm. circular ostium was then fashioned on the dome of the bladder including in it the site of previous re-implantation. The lower end of the ileum was then applied

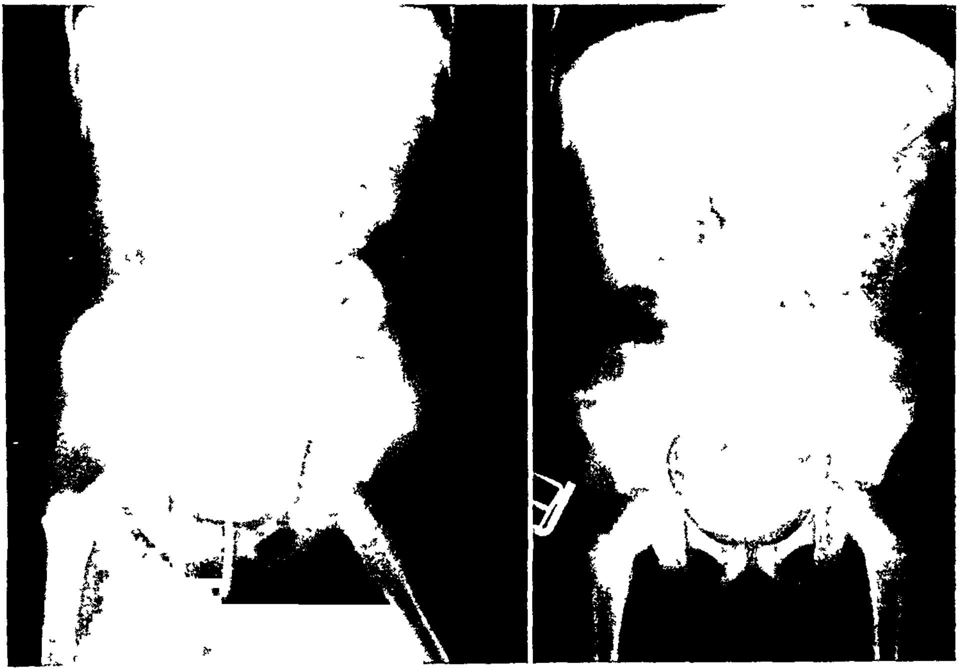


Fig 2

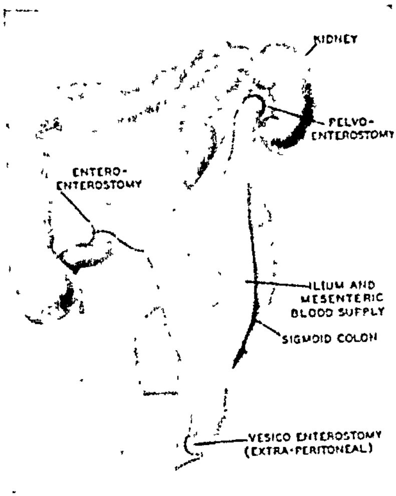

KIDNEY
PELVO-ENTEROSTOMY
ENTERO-ENTEROSTOMY
ILIUM AND MESENTERIC BLOOD SUPPLY
SIGMOID COLON
VESICO ENTEROSTOMY (EXTRA-PERITONEAL)

FIG. 3

directly to this orifice and a two-layer closure accomplished (fig. 3). Urethral catheter and nephrostomy drainage were maintained in the postoperative period. The immediate postoperative course was uneventful.

Before removing the nephrostomy tube detailed fluoroscopic studies were made of the peristaltic activity of the new ureter by injection of radio-opaque medium through the nephrostomy tube. The speed of forward propulsion of the bolus of fluid was remarkable and was recorded in a series of rapid roentgenograms made with the Michigan angiocardiographic x-ray camera (fig. 4). Emptying of the renal pelvis and substitute ureter was accomplished within 10 minutes. Active peristalsis is well illustrated in figure 5 made during a continuous infusion of contrast medium through the nephrostomy tube. Excretory urograms taken at intervals have demonstrated no evidence of change in the pattern of the collecting system on the left. The last study made August 15, 1953, one year after operation, is seen in figure 6. Cystographic studies have demonstrated reflux in all instances, progressive with delay. Thus in figure 7 the 5-minute film shows only the uretero-ileal junction, while over a 30-minute period the entire substitute ureter and kidney are visualized. Fluoroscopic examination of the distended bladder during the act of micturition showed reflux only one-third the distance of the ileal segment. Cystoscopy reveals an adequate ostium in the dome of the bladder.

In an effort to demonstrate the presence or absence of chemical imbalance the electrolyte pattern of the blood was recorded before and at intervals after operation (fig. 8). No significant changes have been noted. Her two hour excretion of phenosulfonphthalein has improved.

The patient has had three episodes of pain in the left flank associated with

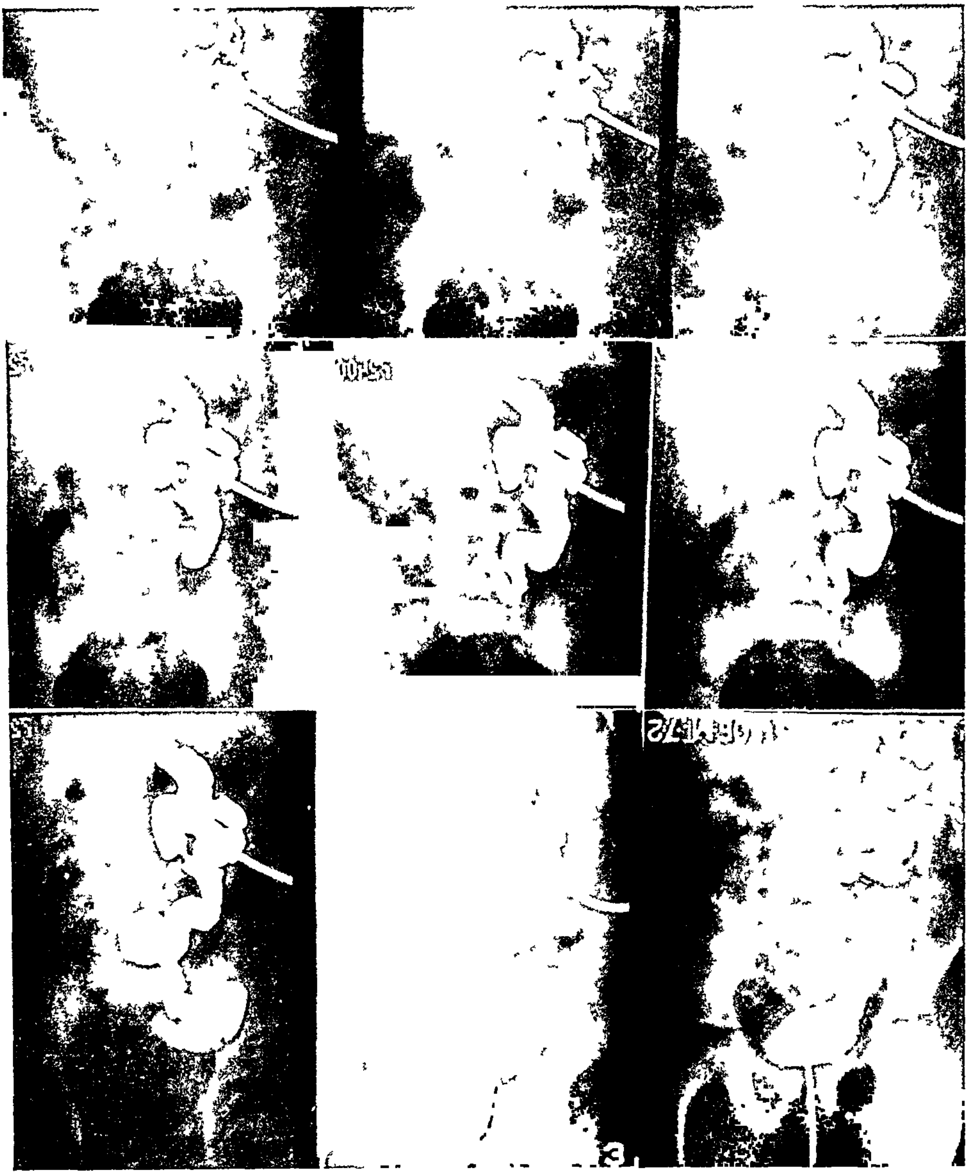


FIG 4

low grade fever in the year of follow-up. The urine has gradually cleared of mucus and now shows but 5–6 white blood cells per high powered field. Efforts to sterilize the urine on the basis of culture and sensitivity studies have been but temporarily effective. Despite the relatively few white blood cells noted, the urinary sediment will grow a number of gram negative bacilli, at least two of which were present preoperatively and were at that time themselves resistant to available antibacterial agents.

Case 2. M. P., 740692, a 33-year-old woman, was admitted to University Hospital on November 26, 1952 with a 6-year history of intermittent bouts of left renal colic. Two weeks prior to admission a left ureterolithotomy was attempted by her physician in an effort to recover an impacted left lower ureteral

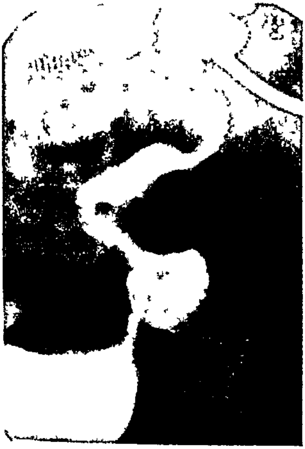


FIG. 5

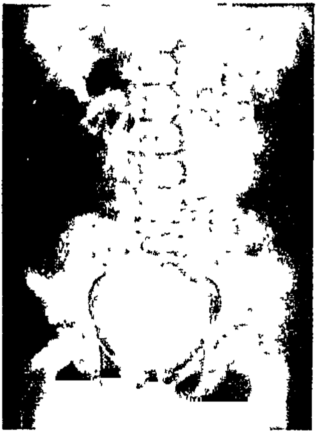


FIG. 6

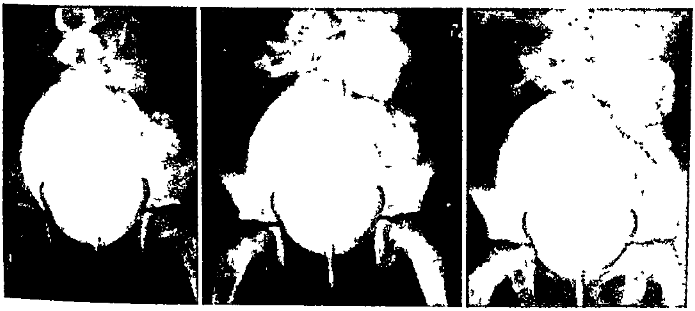
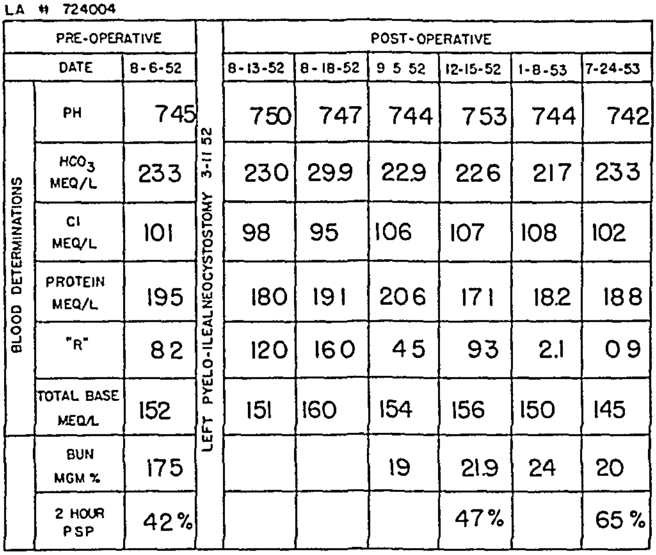


FIG. 7

calculus. This proved unsuccessful, and in the postoperative period the patient drained the majority of her left renal output from her wound. Excretory urograms on arrival revealed a left hydro-ureter and hydronephrosis above a left lower ureteral stone. Retrograde catheterization of the left ureter was impossible. Bulb injection revealed local extravasation of contrast medium (fig. 9). Blood determinations for calcium, phosphorus, alkaline phosphatase and nonprotein nitrogen were normal. A left ureterolithotomy was performed on December 1 with recovery of a soft calcium phosphate calculus. The entire lower one-third of the ureter was found to be encased in dense inflammatory reaction with definite narrowing of the caliber of the ureter in the area of the calculus. An intubated ureterotomy was accomplished utilizing a 10F soft rubber catheter. Following its removal one month later the patient functioned satisfactorily for 48 hours and then again drained all of the left kidney output through her



LA # 724004

PRE-OPERATIVE				POST-OPERATIVE					
DATE		8-6-52		8-13-52	8-18-52	9 5 52	12-15-52	1-8-53	7-24-53
BLOOD DETERMINATIONS	PH	745	LEFT PYELO-ILEALNEOCYSTOSTOMY 3-11 52	750	747	744	753	744	742
	HCO3 MEQ/L	233		230	29.9	22.9	226	217	233
	Cl MEQ/L	101		98	95	106	107	108	102
	PROTEIN MEQ/L	195		180	191	206	171	18.2	188
	"R"	82		120	160	45	93	2.1	09
	TOTAL BASE MEQ/L	152		151	160	154	156	150	145
	BUN MGM %	175				19	21.9	24	20
	2 HOUR PSP	42%					47%		65%

FIG. 8

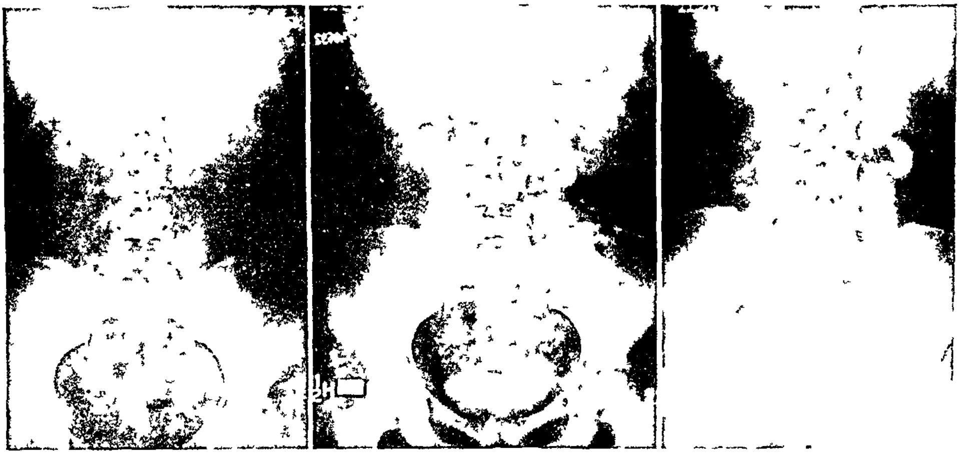


FIG. 9

wound. Repeat pyelograms on January 2, 1953 demonstrated a ureteral stricture with hydronephrosis. The bilaterality of her calculous disease made renal salvage imperative. The extent of involvement made re-implantation or reconstruction an impossibility. Accordingly, a left uretero-ileal-neocystostomy was proposed.

The patient was operated upon January 15. In this instance a 20 cm. loop of terminal ileum was chosen 7 cm. from the ileocecal junction, isolated with its mesenteric blood supply intact, closed at its superior end with a double layer of sutures and anastomosed intraperitoneally to a 3 cm. ostium created in the dome of the bladder. A double layer of sutures was again utilized. The left ureter was then brought from its retroperitoneal bed and applied to the bowel by the direct elliptical method of Nesbit (fig. 10). Nephrostomy was not performed. The patient remained on urethral catheter drainage for 10 days postoperatively and made an uneventful recovery. Her subsequent course was

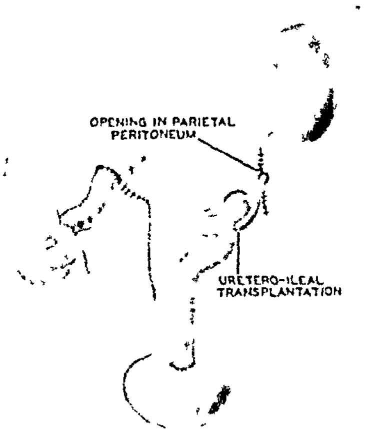


FIG. 10

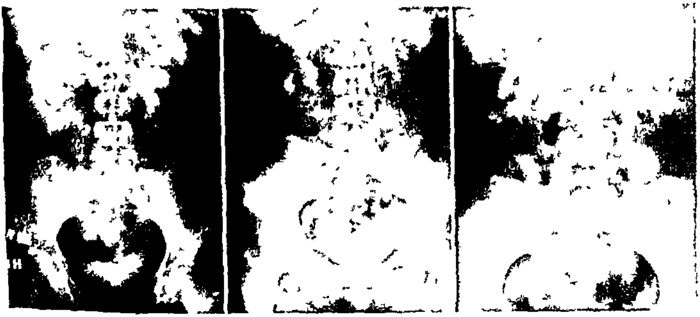


FIG. 11

marred by complications incident to migrating right renal calculi necessitating a right pyelolithotomy and nephrostomy on March 5 and right ureterolithotomy on April 23. At present the patient is in excellent physical condition, has been free from all sepsis and asymptomatic for a period of 4 months.

Excretory urograms made on the third and fourth month after the uretero-ileal-neocystostomy, and incidentally during the period of migration of her right renal calculi, show a satisfactorily functioning left kidney, as does her last pyelogram made on July 9, 1953, seven months after operation (fig. 11). Cystographic studies demonstrate no reflux on the initial distention film (fig. 12), but again with delayed exposures show retrograde passage of contrast medium into the upper third of the substitute ureter (fig. 13). Cystoscopy on July 10 has demonstrated a patent anastomosis in the dome of the bladder.

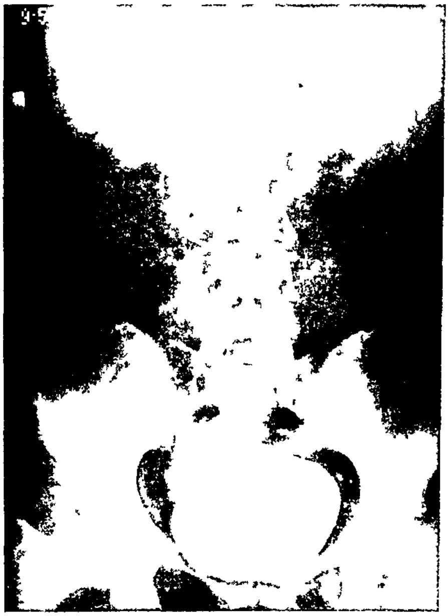


FIG 12

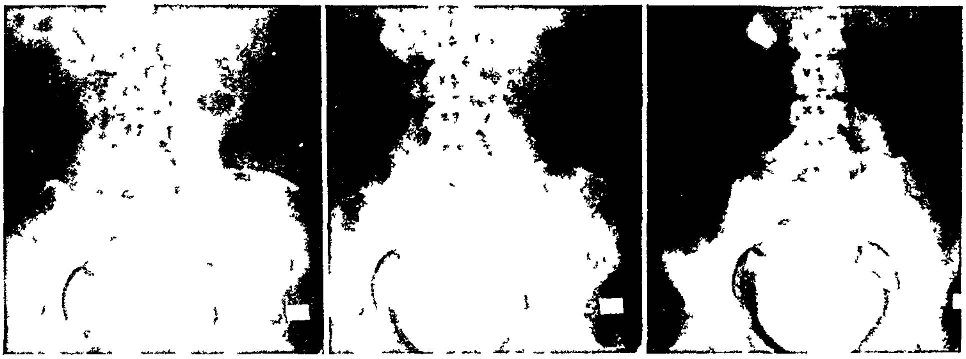
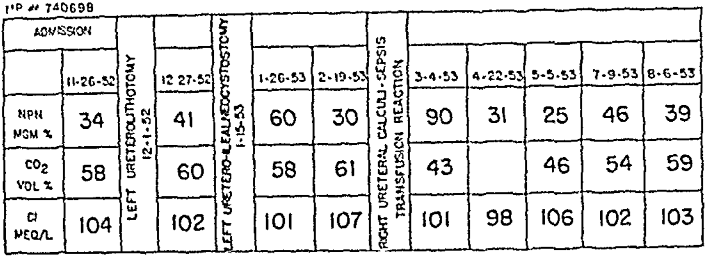


FIG. 13

Examination of postoperative blood chemical determinations (fig. 14) reveals the transitory rise in nonprotein nitrogen which has followed all of these operations. The secondary increase in nonprotein nitrogen noted on March 3, 1953 followed a bout of right pyelonephritis associated with the obstructing right ureteral calculi and a severe transfusion reaction. In the 8 months of follow-up there has been no persistent evidence of acidosis or hyperchloremia. Her last determinations on August 6, 1953 were within normal limits.

The urine now shows a trace of albumin, 3–4 white blood cells per high powered field on centrifuged specimen, and after antibiotic therapy the Aerobacter aerogenes culturally present before and after operation is now absent.

Case 3. R. G., 730750, a 50-year-old woman was admitted to University Hospital in July 1952. She had been investigated 1 year prior to this admission and at the time was found to have a left renal calculus and left hydronephrosis associated with a stricture at the ureteropelvic junction. The right kidney was found to be nonfunctioning. In July 1951 a left pyelolithotomy and pyeloplasty



I.P. # 740698

ADMISSION													
	11-26-52	LEFT URETEROLITHOTOMY 12-1-52	12 27-52	LEFT URETERO-ILEAL-CYSTOSTOMY 1-15-53	1-26-53	2-19-53	RIGHT URETERAL CALCULI-SEPSIS TRANSFUSION REACTION	3-4-53	4-22-53	5-5-53	7-9-53	8-6-53
NPN MGM %	34		41		60	30		90	31	25	46	39
CO_2 VOL %	58		60		58	61		43		46	54	59
Cl MEQ/L	104		102		101	107		101	98	106	102	103

FIG. 14

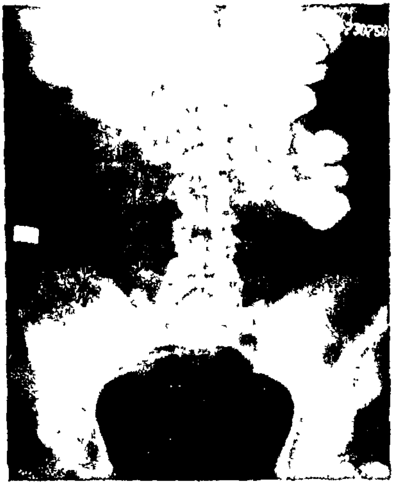


FIG. 15

with associated nephrostomy had been performed. A second operation followed in November 1951 in an effort to correct a persistent stricture. This, too, failed, and the patient was left on nephrostomy drainage.

Admission studies found the patient in good general condition with a satisfactorily functioning nephrostomy, moderate impairment of total renal function, and roentgenographic evidence of a high grade stricture at the ureteropelvic junction (fig. 15). On August 11, 1952 an intubated ureterotomy was carried out, bridging an area of stricture approximately 1 cm. in length just below the renal pelvis. After two months of intubation the polyethylene splint was removed with satisfactory passage of urine from renal pelvis to bladder for a period of three days, then again complete obstruction necessitating return to nephrostomy drainage. Retrograde catheterization was accomplished with a 6F ureteral catheter, and the stricture bypassed but no change in function ensued (fig. 16). The patient was again discharged on nephrostomy drainage.

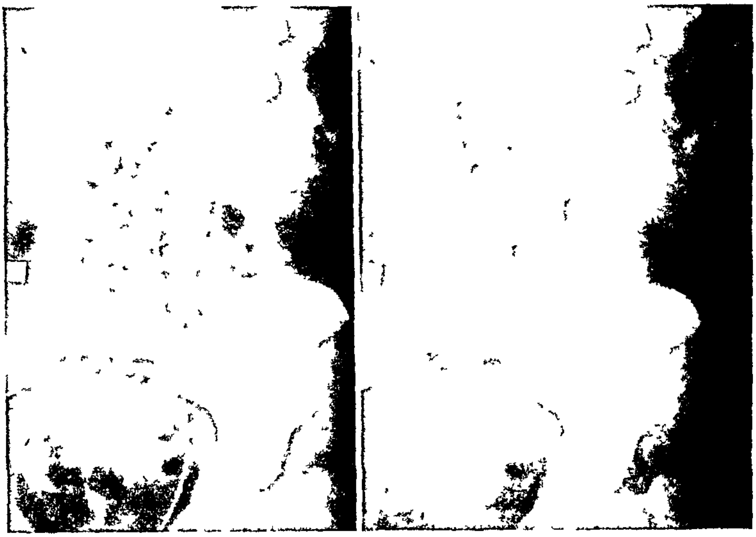


Fig 16

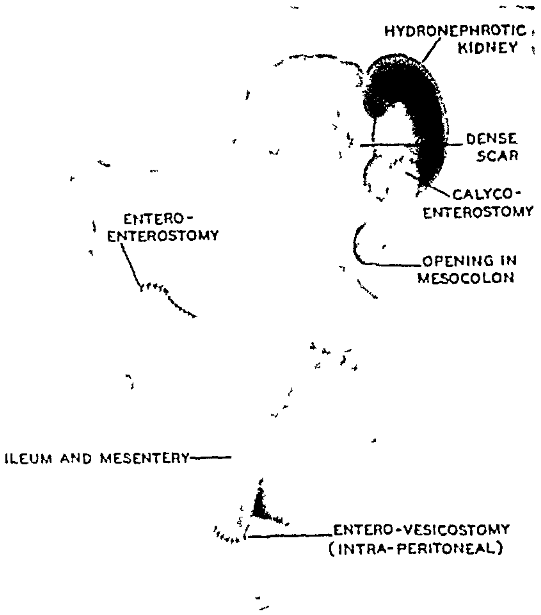


Fig. 17

On her return on January 12, 1953 the situation was found unchanged. The patient had had several bouts of severe sepsis, and had become increasingly intolerant of her nephrostomy tube. She requested consideration of further surgery. The extent of perinephric and peri-ureteral inflammatory reaction noted at the last operation was considered a contra-indication to further uretero-pelvic reconstruction. A pyelo-ileal-neocystostomy was proposed as a reasonable solution to the problem.

On February 9, 1953 the patient was operated upon and exposure of the renal pelvis carried out. It was evident at once that the old inflammatory reaction present would preclude a satisfactory anastomosis between renal pelvis and ileum. The kidney was very large, and the renal parenchyma reasonably thick except near the lower pole opposite a dilated calyx. A circular window was cut in the renal parenchyma at this point approximately 3 cm. in diameter exposing the calyx. A 40 cm. segment of terminal ileum was then isolated as in previous operations, its upper end passed through an opening created in the mesocolon, and the bowel anastomosed directly to the lower pole of the kidney. A two layer closure was utilized applying mucosa of bowel to the calyx, while serosa and muscularis of bowel were sutured to renal parenchyma and capsule (fig. 17). The lower end of the ileal segment was anastomosed intraperitoneally to an ostium created in the dome of the bladder as before. Urethral catheter and nephrostomy drainage were maintained.

The patient made an uneventful recovery. In the next two months she drained the majority of her urine through the nephrostomy tube, and only sporadically passed urine in 50–100 cc amounts by way of the urethra. Clamping the nephrostomy tube did not augment the bladder output, and resulted in pain and sepsis. A cystogram (fig. 18) demonstrated adequate retrograde passage of contrast medium into the kidney. Methylene blue placed in the bladder could be recovered with the patient in moderate Trendelenburg position from the nephrostomy tube within a short time. Injection of the nephrostomy with radio-opaque material failed, however, to show passage of the liquid beyond the anastomotic site. The patient was discharged on nephrostomy drainage. On May 15 the patient's husband inadvertently pulled out the nephrostomy tube. In the interval between this episode and her return to the hospital it became

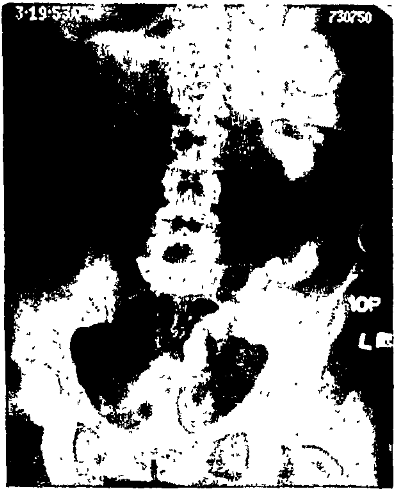


Fig. 18

evident that she was passing the majority of urine through to the bladder. The nephrostomy wound healed and on her last check-up examination on August 8, 1953, she appeared clinically well, had had no sepsis or pain, and was possessed of normal urinary function.

Blood chemical determinations (fig. 19) have demonstrated a moderate elevation in nonprotein nitrogen compatible with her chronic pyelonephritis since admission. Follow-up studies over a 6 month period have shown no real change. Carbon dioxide combining power and blood chloride have also remained essentially within preoperative levels, although the last determination on August 8, 1953 showed a tendency toward hyperchloremia and slight acidosis.

Her urine remains infected with the same organisms isolated prior to operation. They are insensitive to available antibacterial agents and have resisted those which have been administered.

Case 4. E. C., 728347, a 31-year-old woman was admitted to the Medical Service of University Hospital on November 9, 1952 with a diagnosis of malignant hypertension. Fifteen months prior to this admission she had received

RG # 730750

PRE-OPERATIVE		OP	POST-OPERATIVE				
BLOOD	2-6-53	2-9-53	2-11-53	2-16-53	5-20 53	6-15-53	8-8-53
NPN MGM %	51	LEFT CALYCO-ILEAL NEOCYSTOSTOMY	53	51	46	53	56
CO_3 VOL %	58		55	53	53	56	47
Cl MEQ/L	107		101	104	107	106	109

FIG. 19

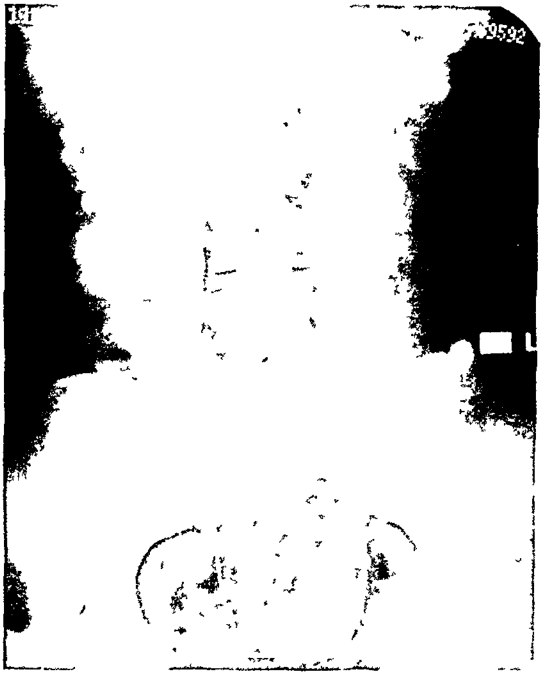


FIG. 20

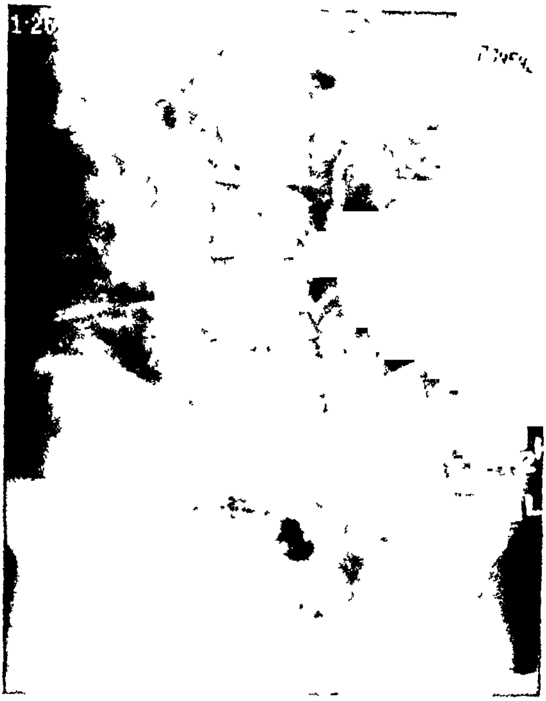


FIG. 22

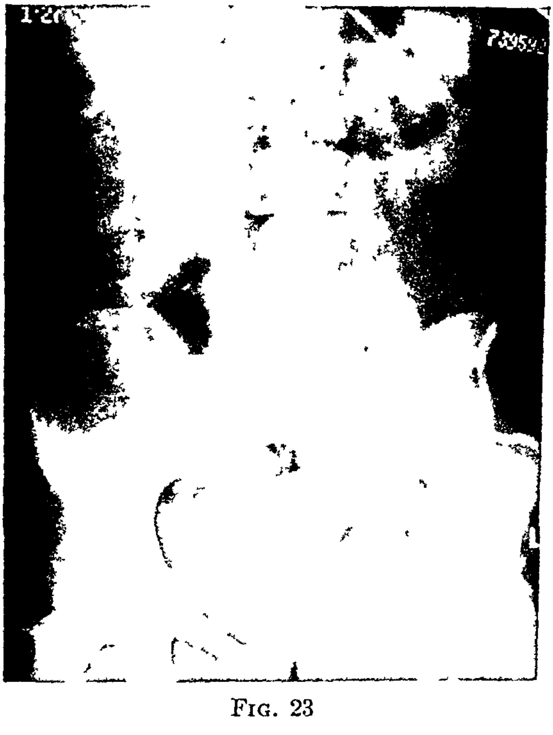


FIG. 23

retroperitoneal gutter. No masses could be felt, but to ascertain the nature of the process a piece of tissue was taken for microscopic examination. It proved subsequently to be neoplasm metastatic from the cervix.

The patient made an uneventful recovery. Intravenous pyelograms three

EC # 728347

	ADMISSION 11 8 53	LEFT URETEROSTOMY IN SITU 11 13 53	11 14 53	1 6 53	1 8 53	24 53	RIGHT URETEROSTOMY IN SITU 11 29 53	12 1 53	2 4 53	2 0 53	7 9 53	BILATERAL URETERO ILEO CYSTOSTOMY 1 6 53	1 8 53	1 14 53	1 20 53
NPN MGM %	192		198	141	163	168		154	62	54	35		67	44	39
CO_2 VOL %	42		37	49	53	54		54	60		56		57	46	
Cl MEQ/L	93		96	88	92	88		110			99		95	95	

FIG 21

weeks after operation demonstrated a normal left kidney There was a moderate right hydronephrosis (fig 22) A cystogram revealed reflux on the one hour delayed film into the bowel, but not involving either kidney or ureter (fig 23) Blood chemical determinations revealed a transient rise in nonprotein nitrogen (fig 21)

Unfortunately, circumstances necessitated the patient's discharge from the hospital before completion of her follow-up studies Her physician followed her in a local institution until July 13, 1953, the date of her demise from metastatic cervical carcinoma He reported no elevation in blood nitrogen and a satisfactory urinary output with freedom from sepsis until her death

DISCUSSION

Logical consideration of the usefulness of small bowel in the manner described may be encompassed by three questions first, is the procedure mechanically sound and technically feasible? second, does the absorption of urinary constituents constitute a hazard of sufficient degree to contra-indicate the procedure? and third, does the bacterial flora of the section of gastro-intestinal tract utilized place the intact upper urinary tract in jeopardy by reason of *ascending pyelonephritis*?

In answer to the first query, it appears evident that terminal ileum may be utilized to by-pass loss of ureteral continuity in those instances where more conservative measures are not applicable There is no doubt that the peristaltic activity observed provides an effective propulsive force for the passage of urine from kidney to bladder It is true that the patency of anastomosis at the ileo vesical junction is secured at the expense of reflux, but the adverse hydrostatic pressures engendered may be in part taken up by the natural redundancy of bowel and thus spare the kidney This appears applicable on the basis of cystographic studies provided too long an interval between acts of micturition does not ensue It would seem unwise to sacrifice patency of anastomosis in the hope of constructing a valve like mechanism at this level, if such were technically feasible Experimental work indicates that the successful use of small bowel as a conveyer of urine is dependent on the rapid progress of urine through it, and not on its function as a reservoir

The second question involves consideration of the stigma of rapid death from chemical imbalance placed on laboratory animals subjected to uretero upper intestinal anastomosis by early investigators From animal and human experiments already referred to it would appear that this situation is noted only when the ureter is placed in the intact small bowel, i.e., a segment not divorced from gastro-intestinal continuity. Such a circumstance, of course, bathes large areas of absorbing mucosal surface for long periods of time with urine. It is reasonable to assume that this would eventually result in a situation incompatible with existence. When, however, reasonable segments of small bowel are utilized, and these are taken from intestinal continuity, the hazard is greatly decreased, especially if one end of the segment is exteriorized. These four cases, together with the clinical references already cited, show, in addition, that anastomosis of bowel to bladder to re-establish continuity of urinary flow does not add to the hazard. There is no doubt that absorption of urinary constituents can and does occur when urine is in contact with small bowel. It is reasonable to assume that time in contact and surface area covered are two of the major factors which determine the degree of absorption. Fluoroscopic studies indicate that the natural response of the small bowel to distention with fluid introduced via nephrostomy is one of rapid progression of the bolus into the bladder through peristalsis. If patency of anastomosis both at the upper and lower aspects of the intestine can be technically accomplished and maintained, and the intervals between acts of micturition reduced to short but reasonable periods of time to avoid reflux, then a minimum of contact may be expected. That such is the case here may be concluded on the basis of blood chemical determinations made. The observations of Lapides indicate that the azotemia and hyperchloremic acidotic syndrome seen in patients following uretero-intestinal anastomosis is most marked and occurs soonest in those with previous renal tubular damage. It is of interest that in all of the cases presented this factor was present through either infection, obstruction, or both prior to operation. Except for one case (R. G. 730750) the only evidence of chemical imbalance was a transient elevation in nonprotein nitrogen. It is realized that this assumption is based on follow-up studies of one year or less, and that considerably more time and greater numbers of patients will be required before categoric statements may be made. The trend, however, is of interest.

The third question involves consideration of the fact that attempts to sterilize permanently the intact or isolated segment of small bowel have not been successful, in man or in laboratory animals. Temporary suppression of intestinal bacterial content has been possible with many of the newer antibacterial agents, but with cessation of therapy, or in some instances, even while therapy is continued, the bacterial count again rises with resistant strains predominant. All of the cases observed here had had urinary tract infections of varying degrees of severity prior to operation. In three instances the same organism, as well as other organisms, was isolated by culture in the postoperative period as was found preoperatively. In only one case was the urine postoperatively free from bacteria culturally, and that only shortly after cessation of antibiotic therapy. It is of interest to note that despite bacteriuria, pyuria was limited in three cases to but 4–5 white blood cells per high power field in the centrifuged specimen. Perhaps a better criterion of potential hazard is not the cultural presence of bacteria, but the clinical history of the patient following the use of ileum as a substitute ureter. Perhaps freedom from pain and sepsis, and maintenance of a normal or constant renal function over a long period of time would provide a more satisfactory means of evaluation. It is conceivable that the presence of bacteria normally endemic to bowel might not prove dangerous as long as patency of anastomosis allows rapid progress of urine without stasis, and micturitional habits prone to allow reflux are avoided.

CONCLUSION

The use of terminal ileum as a substitute ureter to replace gaps in continuity impossible to bridge by more conservative techniques appears reasonable. The successful reported clinical experience of European and American surgeons should be augmented by more detailed study of the chemical and bacteriological problems involved before the procedure can be universally recommended to augment and/or replace established methods.

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MANAGEMENT OF CATHETERS IN A BILATERAL CUTANEOUS URETEROSTOMY

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It is not the purpose of this paper to raise the question of ureterosigmoidostomy versus cutaneous ureterostomy. The advantages, disadvantages, and indications for each of these methods of urinary diversion are well established at this time and are known to all urologists. Where we believed that a cutaneous ureterostomy was indicated, the apparatus described in this article has served well its purpose of making life more bearable to the patient and allowing him a minimum of inconvenience. The advantages of the cutaneous implant over the sigmoid implant are basically the absence of complications usually associated with the sigmoid operation. These are, briefly, 1) the relative simplicity of the procedure; 2) the absence of a long, technical abdominal operation; 3) the absence of the danger of ascending fecal contamination; 4) absence of a postoperative hydronephrosis, and lastly, 5) absence of an electrolytic imbalance from re-absorption of urine from the bowel. There is also one other advantage, namely, accessibility of the kidneys for irrigation and study, if necessary, which procedure is not possible following a ureterosigmoid operation. Once done, the latter condition is permanent and the kidneys are forevermore unavailable; the exception to this statement being, of course, a reoperation and disconnection of the anastomosis to the bowel and re-implanting of the ureters to the skin,—a rather tedious and difficult operation. We have had to do such a breakdown only twice on our service: one for a bilateral ureteral stenosis and impending uremia, and the second in a patient with increased nonprotein nitrogen and severe electrolytic imbalance, but with good functioning ureteral-bowel ostia. Both cases improved immediately and definitely after the ureters were transferred from the bowel to the skin.

There are three common disadvantages of the cutaneous implant technique which are all more or less matters of inconvenience, whereas complications from the sigmoid implants may become matters of life and death. These disadvantages are as follows: 1) the necessity of wearing leg urinals; 2) the inconvenience of continual care of the ureteral catheters, or, if catheters are not used, the danger of a ureterocutaneous stenosis; and 3) the limitations of physical activity due to cumbersome apparatus and leaking connections.

The apparatus described here (fig. 1, *A*) will nullify to a great degree the last of these mentioned. In brief, the apparatus consists of an elastic abdominal support or belt with stays and a zipper connection to allow for easy application

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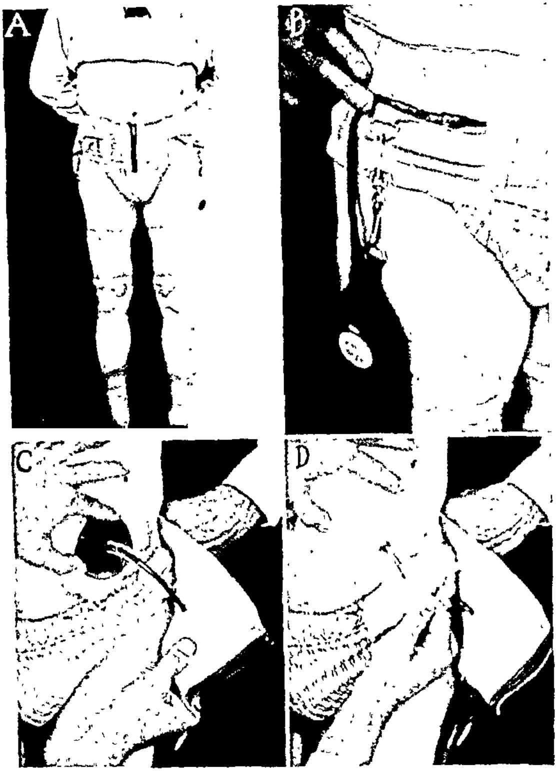

FIG. 1. *A*, complete apparatus. *B*, close-up of swivel connection. *C*, disc being held in place by slit in belt. *D*, 18F straight latex catheter entering ureteral orifice.

and removal. Slits are added in the proper place on each side, depending on the location of the cutaneous implant. These slits are thoroughly hemmed to prevent unravelling of the elastic material. Three-inch latex retention discs (not cups) hold the catheters at the proper length in the ureters. If the proper disc opening is selected to fit the catheter used, then tape will not have to be used to hold the catheter to the disc, as it will fit snugly in the short tube connected to the disc. When the slit in the belt is placed over the nozzle of the disc holding the catheter (fig. 1, *C*) the belt then presses the disc against the abdomen and holds it firmly in place, preventing motion. Swivel clips similar to those used on a dog leash are attached to the belt on each side and allow for support and quick removal of the urinal bags, one of which is worn on each leg. Physical exercise is not only possible, but is carried out with a minimum of inconvenience (fig. 1, *B*).

The case history of the subject seen in the accompanying photographs is hereby

FIG. 2. Preoperative excretory urogram shows filling defect of left bladder wall, nonfunctioning left kidney and hydronephrosis of right kidney.

briefly reviewed. The case of a man aged 62 was diagnosed as carcinoma of the bladder, large meaty, infiltrating type, with multiple lesions in the mucosa. The patient's health had been poor for the past year. He had had backaches and hematuria. Pyelograms showed a bilateral hydronephrosis with a nonfunctioning left kidney (fig. 2). The preoperative nonprotein nitrogen was 60; creatinine 1.5; red blood cells 4,000,000; indigo carmine moderate blue color from the right kidney, only a faint trace on the left. Bilateral cutaneous ureterostomy was done at the first operation and a cystectomy at a second operation one month later. The bladder wall was thick and meaty in places, but it had not been penetrated. The entire bladder, prostate and vesicles were removed in one piece without tearing or opening the bladder wall. There was no evidence of extension to the pelvic glands. He left the hospital and continued his work as a real estate appraiser, working 6–8 hours a day and driving his car daily. He takes care of and cleans his own catheters. He returns to the hospital every month or two for a check-up, at which time his urine is checked and antibiotics are given from time to time for recurrent pyuria. In spite of this moderate pyuria from his original hydronephrosis, his health is excellent.

A retrograde pyelogram 1 year postoperative showed some shrinkage of the original bilateral hydronephrosis. The left kidney function has returned somewhat, but not significantly. His nonprotein nitrogen stays at 42 mg. His right kidney, even though hydronephrotic, is apparently doing most of the work. The output from the left kidney is one-tenth that of the right. One and one-half years following his operation a staghorn calculus developed in his right, or good kidney. (This was seen as a small stone in the lower pelvis of the right kidney at the time of the cystectomy.) This calculus was removed by pyelotomy and the patient returned to work again. There have been no further complications to date, which, at the time of the conclusion of this paper, is two years postoperatively.

In closing, I wish to say that we have not performed cystectomy in all our patients on whom we have done a bilateral cutaneous ureterostomy, as many of our cutaneous implants were done for palliative reasons. It is interesting to note that once the urine was diverted from the bladder, the rate of growth of the bladder tumor was definitely slowed down and the pain, dysuria and hematuria were immediately relieved in almost all patients.

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INCOMPLETE EXSTROPHY OF THE BLADDER: CASE REPORT

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In a careful survey of the literature we have been unable to find any case of incomplete or partial exstrophy of the bladder similar to the one to be reported, in which the bladder and urethra were virtually intact.

REPORT OF CASE

R. M., a white man, aged 44 years, was admitted to the Ochsner Foundation Hospital because of recent bleeding from the exposed bladder surface in the midline of the lower part of the abdomen. Because throughout his life the patient had been advised that surgical correction of his deformity was not possible, he had not sought medical attention until bleeding occurred. He had enjoyed perfect health all his life and had always been capable of normal physical activity. He had been married for 17 years and was the father of 2 children. He had always enjoyed a normal sex life but with erections he had always noted some dorsal curvature of the penis. He voided in an entirely normal manner with a good stream, there was no hesitancy or difficulty and he had good control. He had no urinary frequency or burning, backache, history of pyuria, hematuria or stone. Occasionally while urinating he would notice a thin tiny stream of urine projecting straight out from the center of the exposed bladder. There was no history of any familial congenital anomalies.

Physical examination revealed a well nourished, well developed healthy man who was well adjusted to his congenital defect and concerned only because of the recent bleeding. He walked with the typical waddling gait associated with the bony deformity involved in exstrophy. The involved area appeared on first inspection to be typical exstrophy of the bladder (fig. 1, *A*). There was divergence of the rectus muscles in the lower abdomen with considerable protrusion of the granular, fiery red bladder in the midline. A typical dorsal groove could be seen extending the length of the penis and there was some chordee. Closer inspection, however, immediately revealed that the presenting bladder surface was the outer aspect of the dome of the bladder rather than the floor and also that there was a normally placed urethral meatus in the center of the glans penis. When the patient voided, a pinpoint opening in the center of the bladder could be seen, which intermittently emitted a tiny stream of urine. The stream through the urethra was normal and control was perfect. The prostate and seminal vesicles were normal on rectal palpation.

Urinalysis yielded entirely negative results. The phenosulphonphthalein renal function test showed 60 per cent in 1 hour and 10 minutes. Calibration of the urethra was normal and cystoscopy revealed an entirely normal bladder of somewhat large capacity with a normal trigone. The ureteral orifices were situated somewhat more laterally than in the normal. The bladder neck was essentially

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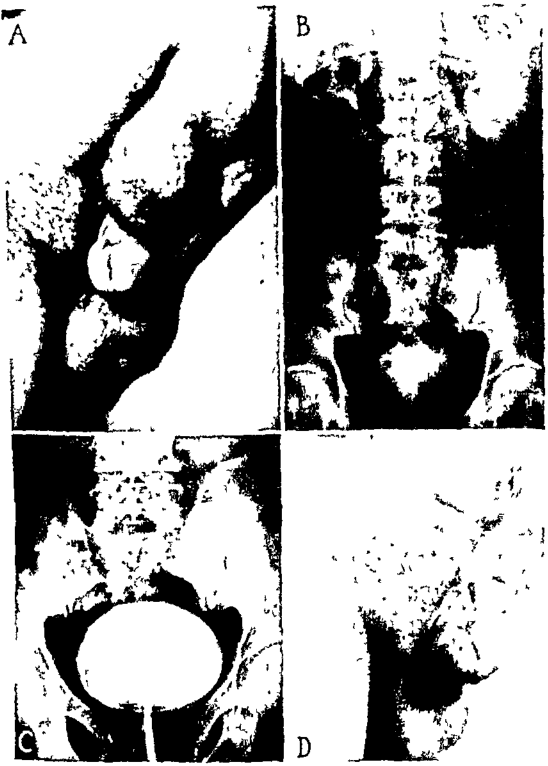

Fig. 1. *A*, preoperative appearance of exstrophy of bladder. *B*, excretory urogram showing normal upper urinary tract. *C*, preoperative cystogram showing characteristic bony defect associated with exstrophy. *D*, postoperative appearance showing almost complete healing.

normal and the prostatic urethra and verumontanum were also normal in appearance. Excretory urograms (fig. 1, *B*) revealed a normal upper urinary tract. A cystogram (fig. 1, *C*) showed only the characteristic bony defects associated with exstrophy. Results of all other essential laboratory studies were within normal limits.

It became obvious that the only treatment indicated was resection of the redundant projecting area of the bladder with subsequent closure of the abdominal wall across the midline. This was accomplished without difficulty. A fairly large segment of the anterior bladder wall was resected after which the remainder of the bladder was sutured and the abdominal wall then closed over it in layers. The pathologic report on the specimen of bladder removed showed nothing more than chronic inflammatory changes. When the patient was last seen three weeks postoperatively the operative wound had almost completely healed (fig. 1, *D*) and he had no urinary complaints.

SUMMARY

A case of incomplete exstrophy of the bladder has been presented which we believe differs in many respects from any other reported cases that we could find in the literature. An unusual feature was the virtually intact bladder and urethra.

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COMPLICATIONS OF NEUROGENIC BLADDER: CASE REPORT

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An extensive urinary phlegmon resulting from rupture of the bladder is still a condition viewed with apprehension by the urologist although the advent of sulfonamides and antibiotics has reinforced his armamentarium. Fatalities have been reported from such a complication in paraplegic patients.[1] It appears justified therefore to report the following case, not only because the patient recovered with a well functioning neurogenic bladder but also because a variety of other urologic conplications was accumulated in one patient, some of which were uncommon.

A 25 year old Negro sustained a fracture dislocation of C-6 and a fracture of D 7 in an automobile accident on June 15, 1946. An extradural hematoma with a rent of the dura was found on early laminectomy. Neurological examination on admission to this center (November 9, 1946) revealed a complete physiologic transection of the spinal cord below the seventh thoracic segment, with marked spasticity of the lower extremities and a loss of bladder and bowel control.

A penoscrotal fistula and a suprapubic cystostomy were present on admission. Shortly after admission a litholapaxy was performed. Thereafter, the penoscrotal fistula was closed operatively while the urinary flow remained diverted by cystostomy. Cystograms revealed bilateral reflux.[2, 3] In March 1947 the suprapubic catheter was removed and within the following 5 months an automatic bladder developed aided by bladder training. The patient was discharged February 1948, but re-admitted in June 1948 with chills, fever, and difficulty in voiding. A stone, 2 cm. in diameter, was found in a diverticulum at the penoscrotal level[4] and removed by means of a lithotrite. The resulting urethral trauma made introduction of a catheter impossible and necessitated another suprapubic cystostomy. From the open bladder a Davis sound helped to introduce an intra-urethral catheter, however, a suprapubic catheter was also left in place. A penoscrotal abscess developed subsequently which, after incision and drainage, healed with resultant tortuosity at the penoscrotal site. This made changing of intra-urethral catheters impossible, therefore, a rubber latex tube was used as a continuous catheter from the suprapubic cystostomy through the urethra and was easily changed at weekly intervals. The patient who became an alcoholic with behavior problems, left the hospital and was discharged A.W.O.L. in July 1949.

He was re-admitted in May 1950 in poor condition with multiple large bed

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[1] Pate, V. A. Jr. and Bunts, R. C.: Faulty healing of suprapubic sinus resulting in fatal peritonitis. J. Urol., 60: 951-51, 1948.

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[3] Hutch, J. A.: Vesico ureteral reflux in paraplegia. J. Urol., 68: 457-467, 1952.

[4] Comarr, A. E. and Bors, Ernest: Pathological changes in urethra of paraplegic patients. J. Urol., 66: 355-61, 1951.

sores and marked loss of weight. The suprapubic cystostomy was closed and an intra-urethral Foley catheter was functioning. In view of the increased spasticity which made the management of the decubitus ulcers impossible a subarachnoid alcohol injection was performed, after the preceding prognostic test by spinal anesthesia had indicated that a good bladder balance would result. Following the alcohol block, this prognosis proved to be correct and a lower motor neuron type of neurogenic bladder developed. With the cessation of spasticity surgical repair of decubiti was possible and the patient was discharged in March 1951.

Two months later, in May, he was re-admitted. He had an intra-urethral catheter which was not draining. He felt that on changing his catheter every other day he had no trouble to insert the catheter adequately into the bladder. He stated that 3 days prior to this re-admission he had slight diarrhea, vomiting and slight abdominal distention. Two days prior to admission his symptoms became worse and his abdomen became more distended. One day prior to admission hiccough developed and vomiting increased. On physical examination the pulse was 120, the temperature 102, respiration 24. The entire abdomen was distended but the lower abdomen more so than the upper. In the region of the old suprapubic scar there was a fluctuant pointing area approximately 5 by 7.5 cm. in diameter with a well demarcated margin. Pitting edema was present suprapubically and extended to both flanks. Infiltration on the abdominal wall could be palpated up to and slightly above the umbilicus. Bowel sounds were audible, but rare. There was a dullness in the right flank, none in the left, but the shift of the dullness on change of position was questionable. An attempt at catheterization of the urethra revealed only a small amount of uriniferous serosanguinous fluid. A cystogram was done immediately which showed marked extravasation anterior to the bladder. A diagnosis was made of rupture of the urinary bladder with extravasation into the space of Retzius and urinary phlegmon of the abdominal wall. The findings at the immediate intervention from a midline suprapubic incision were: necrosis of the subcutaneous fascia, anterior rectus sheath, and rectus muscle. The necrotic mass extended into the posterior rectus sheath and the remainder of the bladder was found at the inferior portion of the necrosed area and consisted of what appeared to be trigone, bas-fond and some remnants of the side walls. The dome was absent. By means of a large metal sound, inserted through the urethra, a rubber tube was introduced as a continuous catheter the ends of which were brought out at the external urethral meatus and the suprapubic opening. Adequate drainage of the abdominal wall was provided and the wound was left open. Gradual granulation closed the large defect so that by June 1951 the suprapubic catheter could be replaced by an intra-urethral catheter. The suprapubic cystostomy was entirely healed by August 1951 and bladder training with tidal drainage were instituted in order to increase the bladder capacity.

On cystoscopy in June 1952 only mild cystitis was found. On urethroscopy three diverticula were seen beneath the trigone, to the right and left, and in the midline. The urethral mucosa appeared fibrotic but the urethra was of an even caliber without evidence of stricture. No reflux could be demonstrated by delayed cystography. Cystometric examination revealed a bladder capacity of 125 cc and in good balance without any residual. The means of voiding corresponds to that of a lower motor neuron bladder, which is a combination of detrusor activity and extrinsic pressure. The intra-urethral catheter was removed because of these findings. The patient left the hospital and was again discharged A.W.O.L.

DISCUSSION

The case presents several interesting features:

The patient survived a rather extensive urinary phlegmon, resulting from extraperitoneal rupture of the bladder. The two fatalities concerning paraplegic patients reported by Pate and Bunts[1] occurred with intraperitoneal urinary extravasation. However it is stated in both instances that previous suprapubic cystostomies were present and were considered contributory to the complication. How much intraperitoneal seepage of urine occurred in our case remains undecided. The shift of dullness on change of position seemed to indicate fluid in the abdominal cavity; but this may have been caused only by transudation and it was not considered advisable to inspect the peritoneal cavity in the presence of an extensive urinary phlegmon of the lower abdominal wall. It is not impossible that this step prevented a further contamination of the peritoneal cavity and was a lifesaving measure. Different stages of extravasation due to faulty healing of suprapubic cystostomies[1] are not common, yet have been repeatedly observed by us. They range from small, pointing suprapubic abscesses, with well walled off sinus tracts to large and deep cavities which need have no demonstrable connections with the bladder, although they originate there. We concur with Pate and Bunts[1] that a low cystostomy is a poor procedure and never perform punch cystostomies in paraplegic patients.

The variety of urologic complications which this single case presents is remarkable. Among the urethral complications the occurrence of calculi is a rare observation even with paraplegic patients and has been observed by us in only two other patients. Formation of diverticula at the penoscrotal junction is common, while those in the prostatic urethra are infrequent,[4] but the occurrence of both in the same case is a rarity. It is mere conjecture, yet not impossible, that in this special case selfcatheterization was the cause of the prostatic diverticulum. This procedure was unnecessary had the patient not displayed psychological traits, not infrequently encountered in paraplegic patients, which lead to self-destruction by willful neglect and which are labeled as a physiological suicide by psychologists.[5] Vesico-ureteral reflux present before administration of a subarachnoid alcohol block disappeared following this procedure, and this is in line with previously reported observations[2] that reflux may be altered by such procedures as pudendal nerve anesthesia or subarachnoid alcohol injections.

It is remarkable that so far amyloidosis could not be demonstrated although multiple decubitus ulcers and severe recurrent infection of the urinary tract were present. Though amyloidosis is not too common it has been repeatedly observed in paraplegic patients.[6, 7]

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[5] Storment, C. T.: Psychological aspects of paraplegic patient. Lecture delivered at Institute of Long Beach Nurses' Association CSNA No. 18, May 14, 1952.

This case demonstrates the instability of "spinal man's" physical health which is the more jeopardized by an unbalanced mental attitude. It is this latter condition which makes the prognosis of this case doubtful.

CONCLUSIONS AND SUMMARY

A case is presented in which the patient recovered from an extensive urinary phlegmon of the abdominal wall, resulting from rupture of the bladder and subsequent extravasation of urine. Various other urologic complications accompanied or preceded the main feature. Since infections of this type originate from suprapubic scars two ways of prevention are possible: either to close operatively all suprapubic sinus instead of permitting them to heal spontaneously[1] or when nonoperative closure has taken place to follow the patient closely and to inform him of the early symptoms and signs of a suprapubic abscess; incision and drainage of the abscess with intra-urethral catheter drainage of the bladder prevents spread with developing phlegmon. After the infection has subsided it is advisable to revise surgically the suprapubic scar of such cases. Correct performance of a high cystostomy will prevent complications of the resultant suprapubic scar.

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BANTHINE AS A UROLOGIC DRUG: A CLINICAL AND ELECTROMYOGRAPHIC STUDY

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The practicing physician is frequently confronted with patients who complain of urinary frequency because of a small bladder capacity. Many of these patients do not have demonstrable genito-urinary disease, and are free of any evidence of central nervous system disease. With the introduction of banthine, as a drug used in the treatment of peptic ulcer, it was noted that an occasional patient complained of difficulty in voiding. Many other patients observed that their voiding efforts were much weaker than before the administration of banthine. Others have observed that they did not void as frequently as they did before they started the drug. Banthine has occasionally precipitated an acute onset of urinary retention in male patients who have slight obstruction at the vesical neck.

These observations led the authors to investigate the effect of banthine on "normal" irritable bladders, i.e. bladders with small capacities having no demonstrable disease. We have also observed the effects of this drug on bladders whose function is disturbed as a result of organic neurological disease or the so-called "neurogenic" bladder.

PHARMACOLOGY OF BANTHINE

Studies on laboratory animals by other writers have indicated that banthine acts as a ganglion blocking agent on both the sympathetic and parasympathetic autonomic nervous systems. It also exerts a potent additive atropine-like action at the post-ganglionic nerve endings of the parasympathetic system. Such effects with reference to the bladder, would be expected to produce a motor paralytic type of bladder, i.e. changes similar to those seen in patients with acute paralytic poliomyelitis.

EFFECT OF BANTHINE ON THE EXCISED RAT BLADDER

Technique. Excised rat bladders were subjected to electromyographic determinations utilizing bathine and acetycholine, with determinations being made before and after the administration of these drugs.

The excised rat bladder was placed in Sollmann's solution, which was surrounded by a water bath at 37.5° centigrade. Electrodes were placed at the fundus and at the trigone of these bladders, and the differences in electrical potential between the electrodes were measured in microvolts. The concentration of banthine in the Sollmann's solution was 0.2 mg. per cubic centimeter of fluid in the bath. More extensive discussion of the technique employed in electromyography of the bladder will be found in other publications.[1, 2, 3, 4]

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[1] Corey, E. L., Boyce, W. H., and Vest, S. A. Fed. Proc., 10: 29, 1951

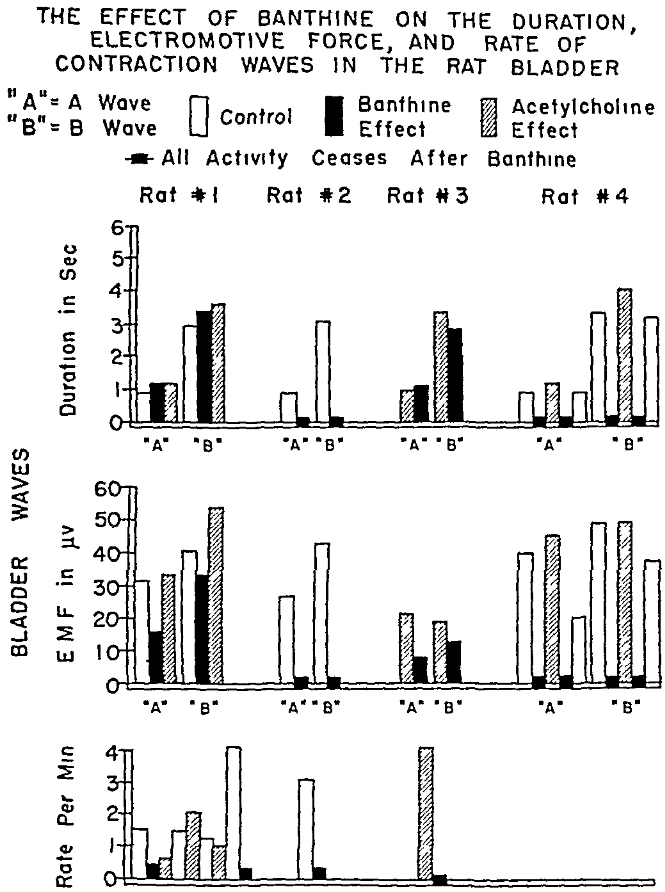

Fig. 1. Force and rate of normal spontaneous changes in electrical potential activity in bladder are consistently diminished or stopped completely by banthine; however, duration of A and B waves is not consistently affected, all activity being stopped in two rats and without effect in other two

Results. Electromyography of the excised rat bladder demonstrated that the electromotive force of the spontaneous A and B waves normally present in the intact and excised bladder[1, 2, 3, 4] were significantly diminished after administering banthine. In addition, the duration of these waves is prolonged, and the frequency of the waves is diminished. Following the use of banthine, acetylcholine will negate the paralytic action of banthine on the bladder. These pharmacological actions are graphically represented in figure 1 and will be reported in greater detail in a subsequent publication.[5]

EFFECTS OF BANTHINE ON THE HUMAN BLADDER

After the administration of intravenous banthine, 1 mg. per pound of body weight, the bladder capacity is often increased in normal patients. Voluntary

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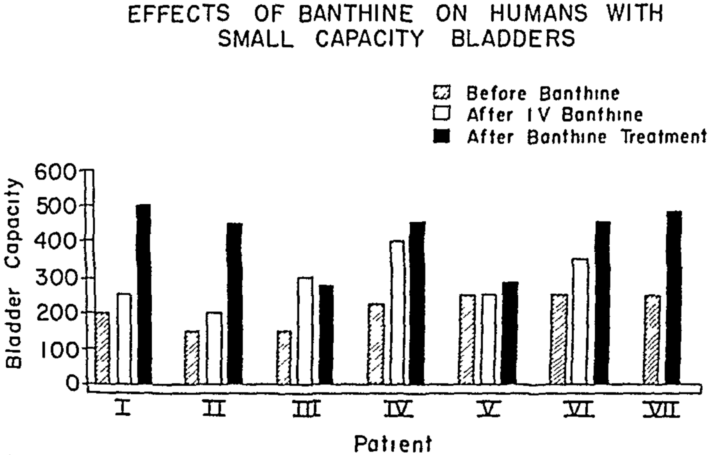

Fig 2 By decreasing parasympathetic activity within bladder wall, banthine caused increases in bladder capacities

effort, in the terms of millimeters of Hg of intravesical pressure, is often cut to 50 per cent of its pre-banthine magnitude

Figure 2 illustrates the changes in the bladder capacities of seven patients with irritable bladders Results of this nature have led us to believe that banthine is the medication of choice for patients with "irritable" bladders of small capacity and without demonstrable organic or neurogenic disease

CLINICAL APPLICATION

The following cases illustrate seven patients with irritable bladders who had no evidence of demonstrable genito-urinary disease, but complained only of urinary frequency We have observed that banthine in such cases will serve to increase the bladder capacities and therefore relieve individuals of urinary frequency

CASE REPORTS

Case 1 Mrs A M, U V H No 53581, a 65 year old Negress, was first seen February 6, 1952 complaining of rather marked frequency and nocturia 3 to 4 times Her urine was entirely negative and cultures were reported as negative Cystometrogram revealed a bladder capacity of 200 cc but was otherwise normal She was given intravenous banthine and 5 minutes later cystometrogram revealed a capacity of 250 cc with decrease in amplitude of bladder contractions and voiding effort Subsequently 50 mg of peroral banthine twice a day reduced her frequency and one week later the bladder capacity had increased to 300 cc One month later, although she stated she was better, her capacity was found to be only 250 cc The dosage of banthine was increased to 75 mg 4 times a day. On July 14, 1952 her bladder capacity was found to be 500 cc with nocturia 1 to 2 times and no frequency during the day.

Case 2. Mr. G. R., U.V.H. No. 321996, a 70 year old Negro, had a transurethral resection of his prostate in 1945 and during the last 3 years he stated that he was having marked urgency, frequency and nocturia 5 to 7 times. Urinalysis was negative. Panendoscopy revealed the absence of further prostatic obstruction. Cystometrogram revealed a contracted bladder with a capacity of 150 cc. Intravenous banthine was administered and 5 minutes later the cystometrogram was repeated with the bladder capacity found to be increased to 200 cc. Again there was a decrease in the amplitude of bladder contractions as well as the intravesical pressure recorded during the voiding effort. He was given 50 mg. of banthine perorally twice a day. He was seen on monthly visits and each time his bladder capacity had increased, finally reaching 450 cc. The patient's symptoms improved although he still had nocturia 2 to 3 times and some frequency.

Case 3. Mrs. A. B., U.V.H. No. 65832, a 48 year old patient, was seen on February 23, 1952 complaining of drawing sensations after voiding, marked frequency and nocturia 8 to 10 times. Urinalysis and physical examination were entirely negative. Cystometrogram showed a bladder capacity of 150 cc with normal bladder tonus. She was then given 100 mg. of banthine intravenously and 5 minutes later her bladder capacity was found to be 300 cc with decrease in the amplitude of bladder contractions. She was placed on 50 mg. banthine 3 times a day and 2 weeks later her bladder capacity was 275 cc with rather marked improvement in her symptoms. Her nocturia was only 1 time with frequency in the day of 5 to 6 times. She was seen one month later with further improvement in her symptoms but unfortunately the bladder capacity was not re-examined.

Case 4. Mrs. M. S., U.V.H. No. 298944, a 70 year old patient, was first seen on September 5, 1951 complaining of dysuria, frequency and nocturia 10 times at night. Her urinalysis was negative. On February 5, 1952 a cystometrogram showed normal findings excepting a bladder capacity of 225 cc. Her symptoms had persisted since her original visit. She was given 100 mg. of banthine intravenously and the bladder capacity was increased to 400 cc with diminution of amplitude of bladder contractions. She was placed on 50 mg. of banthine 3 times a day and on her last visit, the bladder capacity was found to be 450 cc with a frequency 4 to 5 times a day and nocturia 3 to 4 times.

Case 5. Mrs. Z. P., U.V.H. No. 190145, a 60 year old patient, was seen complaining of marked frequency and nocturia 2 to 3 times. Urinalysis was negative. Physicial examination revealed only a senile vaginitis. A cystometrogram was normal except her bladder capacity was found to be only 250 cc. Banthine 100 mg. given intravenously did not result in any increase in bladder capacity, but there was some decrease in amplitude of bladder contractions. She was given 100 mg. of banthine 3 times a day and 1 month later her bladder capacity was found to be 290 cc. She only had to void 3 times a day with nocturia 0 to 1 times. She discontinued banthine and one month later she was having some frequency and nocturia. Her capacity was found to be 250 cc. She was again given the same dosage of banthine and in 3 weeks her bladder capacity was 320 cc without frequency or nocturia.

Case 6. Mrs. E. H., U.V.H. No. 291513, a 39 year old patient, was first seen complaining of urgency, frequency, and burning. Urinalysis showed an occasional white blood cell but otherwise was entirely negative. Cystoscopy revealed no lesions or abnormalities except a bladder capacity of 250 cc. She was given 100 mg. of intravenous banthine and in 5 minutes her bladder capacity was found to be 350 cc. She was placed on 50 mg. of banthine 3 times a day. One month later there were no complaints and bladder capacity was 150 cc. Her last urinalysis was entirely negative.

Case 7. Mrs. G. B., U.V.H. No. 51990, a 19 year old patient, complained of frequency every hour, day and night. Her bladder capacity was found to be 250 cc. She was placed on banthine 50 mg. 4 times a day and two weeks later her bladder capacity was found to be 180 cc, although she was still having frequency of 5 times a day and nocturia of 3 to 4 times. One month later she was still having some frequency but with nocturia reduced to 0 to 1 times.

DISCUSSION

While banthine did not correct the fundamental pathological changes in the aforementioned patients, it did by reducing the parasympathetic activity within the bladder wall, increase the capacity (fig. 2) and render the condition more tolerable.

Additional experience with banthine for patients with "neurogenic" bladders of the uninhibited and spastic type has paralleled that of Lapides and Dodson.[6] The drug will assist patients with such conditions in developing automatic bladders by completely eliminating uninhibited spontaneous vesical contractions and increasing the bladder capacity.

We have also used banthine during transurethral resection of the prostate gland in a patient with a small bladder capacity. Banthine increased his bladder capacity when it failed to increase under the influence of spinal anesthetic. At the beginning of the resection the capacity was 70 cc but this was increased to 170 cc following 100 mg. intravenous banthine, thereby permitting longer periods of cutting before the instrument had to be removed to evacuate the irrigation fluid.

Banthine has proved valuable for pre- and postoperative patients who became uncomfortable from bladder spasm as a result of inlying catheters. These spasms, which are most distressing and frequently cause the patient to void around the catheter are usually eliminated by banthine.

CONTRA-INDICATION TO ADMINISTRATION OF BANTHINE

Banthine is contra-indicated in the presence of glaucoma because of the appearance of mydriasis in some patients. Any patient with lower urinary tract obstruction is a poor candidate for banthine as it may induce acute urinary retention.

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[6] Lapides, J and Dodson, A I. Jr · J. Urol , 69: 96, 1953

CONCLUSION

The authors have found banthine to be of value in treating patients with small and unexplained irritable bladders. It is helpful in the management of spastic neurogenic bladders secondary to disease in the central nervous systems.

Patients wearing catheters who have bladder spasms appear to be relieved by the use of banthine.

It is also of value in increasing the capacity of small bladders during transurethral resection.

Treatment with banthine is initiated by administering 50 mg. 4 times a day, and if the effect upon the bladder is not remarkable, this dosage is often increased to 100 mg. 4 times a day.

ADDENDUM

Since submitting these results for publication, we have used pro-banthine in similar cases and find that its action is identical with that of banthine. It has the additional advantage of exhibiting few side reactions and possibly a more specific effect on the autonomics innervating the lower urinary tract.

The banthine and pro-banthine used in these experiments were kindly supplied by Dr. J. William Crosson of G. D. Searle and Company.

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GAS GANGRENE OF PENIS AND SCROTUM

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The world literature is malnourished with reported authentic cases of gas gangrene of the penis and scrotum. Aside from the land mine, upward blast type of warfare injury, the genitalia consistently and fortunately escape external mutilation and anerobic bacterial inoculation, when one considers the myriads of accidents to which the general population is subjected daily.

The pathogeny demands initially that the trauma be supplied. Whether or not progression to gas gangrene occurs depends upon the presence of gas forming organisms thriving greedily under conditions of oxygen insufficiency. The bacteria usually implicated are streptococci, staphylococci, color bacilli, and the Clostridium clan. Circulatory impairment and tissue necrosis having been established, the organisms propagate with swift dispatch and sweep forward like prairie fire, disintegrating and blistering fascial planes and tissue barriers, closing blood supply to adjacent parts, leaving their production of gas as if in monument to work done. The alarming picture at this stage is familiar to everyone.

Following a history of trauma to the part, there is usually a readily evident break in dermal continuity. Depending upon the stage in which the gangrenous affliction is seen, the patient has some fever, leukocytosis, and swelling and discoloration of the skin. There may be evidence of external necrosis and sloughing with characteristic exudate and odor. Edema and gas, signified by crepitation are the cardinal features. Pain may, or may not, be a subjective complaint.

REPORT OF CASE

Pvt -J, No. 27966, a 19 year old white, previously healthy male, was admitted to the U. S Army Hospital, Camp Gordon, Georgia, February 13, 1952, with a history of painless swelling of the penis and scrotum following an alleged accident 4 hours earlier, in which a small boiler fell on him striking the upper part of the right thigh and falling across the right groin, supra pubic area and genitalia—after an attempt to lift it. By the time he was admitted to hospital, the swelling of penis and scrotum had become painful. There were no other complaints

The urology department was not called in until 6 hours later. At that time, clinical examination revealed a healthy looking young white man, until the covers were pulled down. The temperature and blood pressure were normal. There was no evidence of toxemia and general physical examination, including rectal, was negative, aside from the genitalia. The uncircumcised penis and scrotum were tense, edematous, and the dusky color changes of circulatory. impairment were obvious The testes, epididymides and cords were in position and felt to be normal. There was such a degree of edema that it was impossible to visualize the meatus. Crepitation was noted nearly everywhere. Beyond the penis and scrotum the tissues were not affected. Urine and blood studies were negative.

The patient was taken to the operating room immediately, and a dorsal slit was made. Gas and exudate escaped readily from the cut edges. It was only after careful exploration that the portal of entry was determined. On the ventral, and right hand side of the mucosal surface of the foreskin, there was seen to be an oblique, slit-like wound, ½ cm. long with degenerated purplish colored edges. On squeezing manually up to the opening, a large amount of thick, putrid material revealed itself. The exploring index finger was then introduced, and a wide long sinus tract extended backwards in the long axis of the penis as far as the scrotum. Multiple drainage incisions were then made and Penrose drains inserted all over in through and through fashion. A 18F Foley catheter was inserted and retained. The whole apparatus was supported on a Bellevue bridge.

On culture, hemolytic Staphylococcus aureus and anerobic streptococci were isolated. On smear, gram positive bacilli, morphologically resembling Clostridia were seen.

Postoperatively, the patient was given 300,000 units of procaine penicillin q. 3h., a booster of tetanus, and an ampoule of antigas serum.

By the next day, he had a temperature of 100, and the swelling was considerably reduced. After 48 hours, the temperature fell to normal permanently. On February 16, all drains were removed, and hot saline soaks begun. On February 20, the catheter was removed, he was allowed up and about with a scrotal supporter, and hot sitz baths q. 3h. were initiated. On February 26, he was completely cured and sent to duty.

SUMMARY

A rare and interesting case of gas gangrene of the penis and scrotum is presented. Pathogenesis, signs and symptoms are reviewed briefly.

The patient tenaciously clung to his masterpiece of fabrication involving the boiler. The slit-like break in the mucosal surface of the foreskin was obviously the focal point for the infection. Just how this occurred involves fascinating speculation.

1719 Walton Way, Augusta, Ga.

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POLYORCHIDISM: A CASE REPORT

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The presence of more than two testes in man has excited interest in legendary and historical times. In the ancient literature many cases are described and those thus endowed were believed possessed of supervirility. Great warriors and lovers were said to be thus adorned. The only authentic example in the early years is the autopsy case of Blasius in 1670. Although 3, 4, and 5 testes have been reported only cases of triorchidism are proven.

Lane reported the first histologically proven case in 1895. Boggon, reviewing the literature in 1933, found 11 proven cases and added one of his own. Ten additional cases have been reported to date by Chevassu, Goldstein and Casilli, Cranz, Thiessen, Handley and Crawford, Dardill and Constantini, Ranson, Smith, Evans and Suder, and Lowsley and Porras. Thus a total of 22 cases have been reported. The purpose of this paper is to report an additional case.

Supernumerary testes are seen to be rare. Supernumerary ovaries are also rare Small islands of ovarian tissue in the broad ligament are frequent but Brady could find only 9 proven cases of polyorchidism in the female. Testicular tissue has been found in the adrenal of man and chicken. Multiple testes have been described in man, pig, and chicken.

Embryological explanation of these testicular anomalies is not difficult. The testicle's origin is from the genital ridge on the inner surface of the wolffian body. The epididymis and vas deferens arise from the wolffian body. The anterior seminiferous tubules appear first and normally degenerate, new tubules being formed caudally. Failure of this degeneration to take place anteriorly, while taking place medially, would produce a bipartate organ. Spotty degeneration would account for multiple islands of testicular tissue.

Of the 22 proven cases 12 are on the left and 10 on the right side. As this is a congenital anomaly it is found from childhood to old age. The supernumerary testis is usually palpable as a scrotal or inguinal tumor, rarely as a femoral tumor. It may be an incidental finding at herniorraphy or celiotomy. Boggon's case was associated with recurrent torsion, Goldstein and Casilli's with a rhabdomyosarcoma of the cremasteric muscle. It is usually located proximal to the normal testis and is smaller in size. It is usually equipped with a separate vascular supply, and may have a separate or common epididymis and vas deferens Active spermatogenesis is generally not present but has been reported in some cases Most of the unproven supernumerary testes are in reality spermatoceles, encysted hydroceles, small omental hernias, or tumors of the testis, epididymis or cord, or the vestigal structures connected thereto. The diagnosis should be made only upon adequate histological study.

CASE REPORT

L. V. J., a 23 year old white soldier, was admitted to the hospital on October 9, 1951 for operative therapy of bilateral varicose veins. Past history revealed that a right inguinal herniorraphy had been performed in 1947 and that the patient had had enuresis extending into the early teens.

Physical examination revealed the bilateral varicose veins. Above the normal right testis was located a round, discrete, firm, nontender mass 3 cm. in diameter. The left testicle was normal in position, size and consistency. The patient had never noted this mass before, nor had it been called to his attention by previous examiners.

Routine laboratory studies were within normal limits.

A routine bilateral high-low saphenous vein ligation and stripping was carried out under spinal anesthesia. At the conclusion of this procedure the right scrotum was explored to determine the nature of the mass. The scrotum was opened vertically directly over the mass. This was easily delivered and found to be a testicle 3 cm. in diameter. The other occupant of the right scrotum was then delivered, and to the surprise of the operators, found to be a normal testicle 3.5 cm. in diameter. There was a normal testicle, epididymis and vas deferens palpable in the left scrotum (fig. 1).

The testes on the right side occupied a common tunica vaginalis. Each possessed a separate spermatic cord with veins, artery and vas. These cords showed no tendency toward union as far proximally as the external inguinal ring. They were joined by the normal tunics of the spermatic cord which invested each. There was some thickening of the distal fringe of the tunics which joined the 2 testes.

In view of the possibility of the torsion, the smaller, proximal testis was removed in toto after ligation of its cord. The larger, distal testis was biopsied and returned to the scrotum.

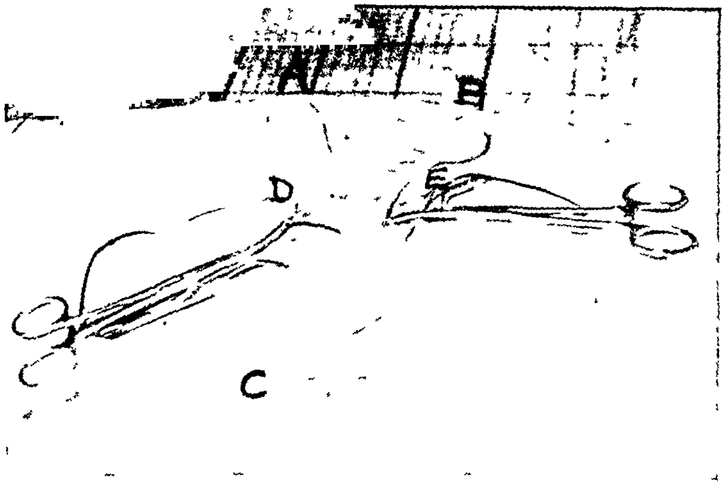

FIG. 1 *A*, normal right testis. *B*, supernumerary right testis *C*, normal left testis. Individual cords to testes on right side can be identified at *D* and *E*.

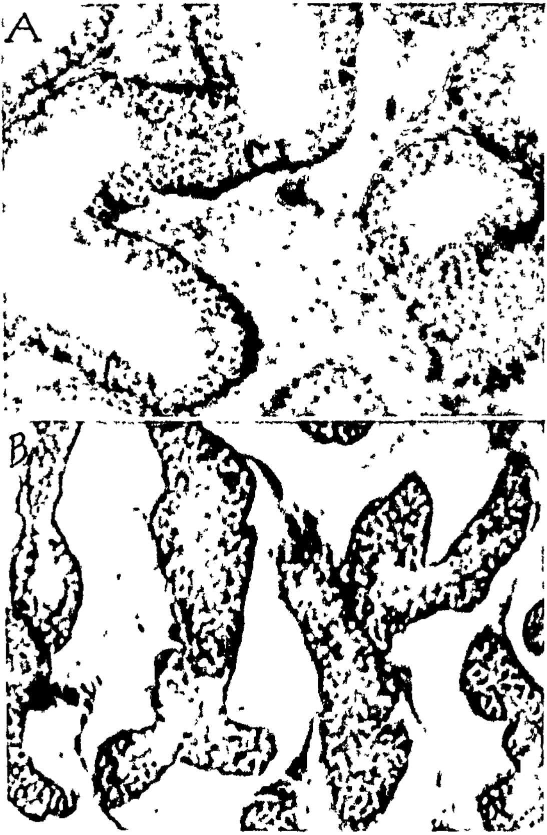

FIG 2. *A*, supernumerary testis *B*, normal testicular biopsy.

The patient had an uncomplicated postoperative course and returned to full duty on the twentieth postoperative day.

Pathological report. The excised testis measured 3.5 by 3.0 by 2.2 cm. and was of normal contour. On cut section the organ was light tan and the tubules strung well. The epididymis was proportionate in size to the testis. The biopsy fragment of the other testis measured 0 8 by 0 7 by 0 2 cm.

Microscopic: Normal testicular tissue was found in both the excised organ and the biopsy specimen. In both specimens spermatogenesis was active (fig. 2, *A*)

SUMMARY

The literature dealing with polyorchidism in man has been briefly reviewed. There are 22 proven cases in the literature. The twenty-third case is added.

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HISTOLOGIC DIAGNOSIS OF CANCER BY STUDY OF BLENDED TISSUES WITH PARTICULAR REFERENCE TO ADENOCARCINOMA OF PROSTATE

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Among the various techniques which have been developed to improve the early diagnosis of cancer of the prostate gland are selective sectioning of transurethral curettings (Satterlee), preparation of numerous sections of curettings (Baron and Angrist), needle biopsy (Ferguson; Melick; Peirson and Nickerson), and cytological procedures (Albers, McDonald and Thompson; Boyer; Chute and Williams; Herbut; Herbut and Lubin; Lewis; Mulholland; Peters; Peters and Young; Schmidlapp and Marshall).

A few months ago it occurred to us that a blending technique might be used for the study of tissue removed by transurethral resection. This has proved a practical method for finding small amounts of carcinomatous tissue.

METHOD

Formalin-fixed curettings are placed in 100.0 ml. of 10 per cent formalin and blended for a period of 2 minutes in a Waring blender of the ordinary kitchen variety (Model FC-1). The blending is somewhat more uniform if the blender is equipped with a fine mesh screen* fitted about 10.0 cm. above its base. We use such a screen surrounded by a rim of one-half inch adhesive tape folded over its edge to fix it in place.

After the two minutes of blending, the mixture is filtered through two thicknesses of No. 12 by 20 gauze. Excess moisture is manually expressed by tightening the gauze about the tissue it contains.

Approximately 4.0 cc tissue are then placed in a receptable and run through dehydrating, fixing and paraffinizing solutions in the same manner as routine surgical tissues. In our laboratory this involves passing through formalin, acetone, acetone-cupric sulfate and paraffin. Sections are stained in routine fashion with hematoxylin and eosin.

RESULTS

To evaluate the method, twenty mixtures of benign and malignant tissue were blended. Each of these mixtures consisted of approximately one part carcinoma-bearing prostate gland and one hundred parts of prostate gland previously diagnosed histologically as benign. The malignant tissue selected was obtained from two patients with moderately well differentiated adenocarcinoma (grade 2) of the prostate gland. Since such lesions are common among malignancies of the prostate gland it was felt that their selection would give fairly typical findings. An average of four sections were made from each mixture.

Presented before International Society of Medical Museums, April 1, 1953

* Available in hardware stores as brass strainer-cloth (mesh 26)

TABLE 1. *Results obtained by blending approximately one part of malignant with 100 parts of benign tissue*

SPECIMEN NO.	NONMALIGNANT PROSTATE		MALIGNANT PROSTATE		NO. OF BLOCKS	NO. OF SLIDES	RESULT
	Amount (gms.)	Portion*	Amount (gm.)	Portion†			
1	25.0	I	0.25	A	1	5	Positive
2	25.0	I	0.25	A	1	6	Positive
3	25.0	I	0.25	A	1	4	Positive
4	25.0	II	0.25	A	2	4	Positive
5	25.0	II	0.30	A	2	6	Positive
6	25.0	II	0.30	A	2	2	Positive
7	25.0	I	0.25	B	2	5	Positive
8	25.0	III	0.275	B	2	2	Positive
9	25.0	IV	0.30	B	1	2	Suspicious
10	25.0	III	0.30	B	1	4	Positive
11	25.0	V	0.30	B	2	5	Positive
12	25.0	VI	0.25	B	2	6	Positive
13	25.0	VII	0.25	B	1	2	Positive
14	25.0	VIII	0.25	B	1	3	Suspicious
15	25.0	IX	0.25	B	1	3	Negative
16	25.0	X	0.25	B	1	6	Negative
17	25.0	XI	0.25	B	1	3	Positive
18	25.0	X	0.25	B	1	4	Positive
19	25.0	XII	0.25	B	1	4	Positive
20	25.0	XIII	0.25	B	1	3	Positive

* The Roman numerals refer to benign specimens, each different number representing a different patient.

† The capital letters refer to malignant specimens, each different letter representing a different patient.

The results are indicated in table 1.

In sixteen of the twenty mixtures malignant tissue was recovered. It was of particular interest that histologic detail of carcinoma was satisfactory (fig. 1). We were pleasantly surprised by this, since the most we originally expected was good cytologic detail. Another helpful finding was that although normal epithelium was often desquamated leaving empty acinar spaces devoid of epithelium, neoplastic acini were frequently relatively better preserved. This appeared to be due to their small size and lack of papillae, plus the intimate association of neoplastic epithelium and supporting stroma.

The histologic criteria of carcinoma utilized in this study were those which have been outlined by McDonald, Moore, Lewis, and Totten et al. namely, small acini, lack of papillae, cytoplasmic vacuolation, absence of basal cells, lack of regular acinar-stromal orientation, large nucleoli and tendency for peripheral clumping of nuclear chromatin. With these criteria in mind lobular hyperplasia such as that recently described by Totten and associates did not present a diagnostic problem.

Encouraged by the preliminary demonstration of the possibility of finding small amounts of carcinomatous tissue, we proceeded to clinical application of

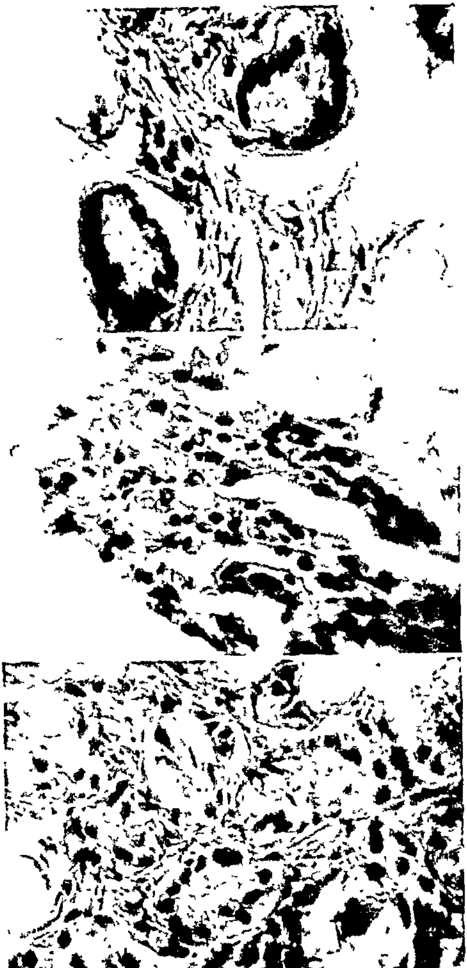

FIG. 1. Fragments of malignant tissue from blended specimens. Satisfactory cytologic s well as morphologic detail is seen.

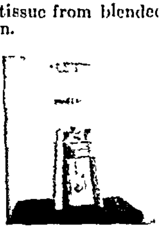

FIG. 2. Waring blender showing wire mesh screen in blending chamber.

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DETECTION OF EARLY PROSTATIC AND URINARY TRACT CANCER IN ASYMPTOMATIC PATIENTS FIFTY YEARS OF AGE AND OVER

A PRELIMINARY REPORT

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The prostatic research project initiated 3 years ago at the Strang Cancer Prevention Clinic of Memorial Center, New York City, was undertaken to evaluate the cytologic method in all asymptomatic patients 50 years of age and over.

An attempt was made to use this method as a routine screening measure in order to determine whether early unsuspected malignancy of the urogenital tract, and particularly of the prostate gland, could be detected in males within the cancer age group and before cancer is clinically evident.

From October 1, 1949 to October 1, 1952, 1738 male patients, 50 years of age and over, were examined at the Strang Clinic.

Clinically suspicious or positive cases were excluded from this study.

Four slides were prepared from each patient: two from prostatic secretion and two from urine sediment. The slides were fixed from one hour to forty-eight hours in the ether-alcohol fixative. The fixed slides were stained by the Papanicolaou method.

Smears obtained after prostatic massage were found to contain a great variety of cells; some were considered as of prostatic origin, others originated from the testes, seminal vesicles and urethra.

The origin and interpretation of many cells still remains a subject for further study.

Glycogenic cells were seen in prostatic secretion of several patients without any history of estrogen therapy and without clinical evidence of estrogen imbalance (fig. 1).

In benign inflammatory conditions, polymorphonuclear leukocytes were often noted in varying numbers as well as an increase in the number of exfoliated cells. In many instances, the cells exhibited atypical features as a result of inflammation. Such cellular changes were often characterized by nuclear enlargement, cytoplasmic vacuolization and alterations in the staining properties of the cytoplasm.

There were a great many cases of nonspecific prostatic infection.

Several cases of trichomonas infection of the prostate gland were diagnosed by the smear.

In our series, we accounted for many cases with atypical cells which did not exhibit malignant features.

Read at annual meeting, American Urological Association, St. Louis, Mo. May 13, 1953.

Several cases were classified as suspicious for malignancy (fig. 2). Finally, few cases were classified as positive for malignancy. Malignancy was noted in single cells or in clusters of cells.

An early unsuspected carcinoma of the prostate gland was detected by the cytologic method in a 58-year-old man. The prostatic smear showed a single cluster of three enlarged, overlapping, moderately hyperchromatic nuclei (*fig.* 3, *A* and *B*).

This patient was operated on and the pathologic report of serial sections of the prostate gland was early tubular carcinoma (fig. 3, *C* and *D*).

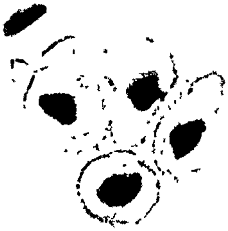

FIG. 1. Glycogenic cells

This unsuspected preclinical cancer of the prostate gland was detected primarily by the cytologic method and correlation between the cells on the smear and section was obvious.

Smears from voided urine, after prostatic massage, were found to contain a variety of cells similar to those found in the prostatic secretion mixed with cells originating from the transitional epithelium of the bladder, ureters and renal pelvis.

Cells exfoliated from very early preclinical cancer of the bladder may exhibit

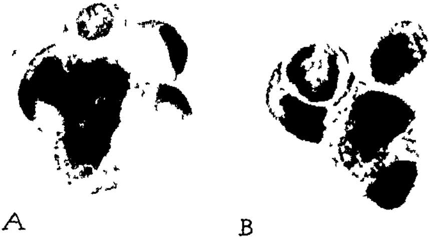

FIG. 2 *A*, cluster of atypical cells in rosette form suspicious for malignancy. *B*, cluster of atypical cells with irregular, hyperchromatic nuclei

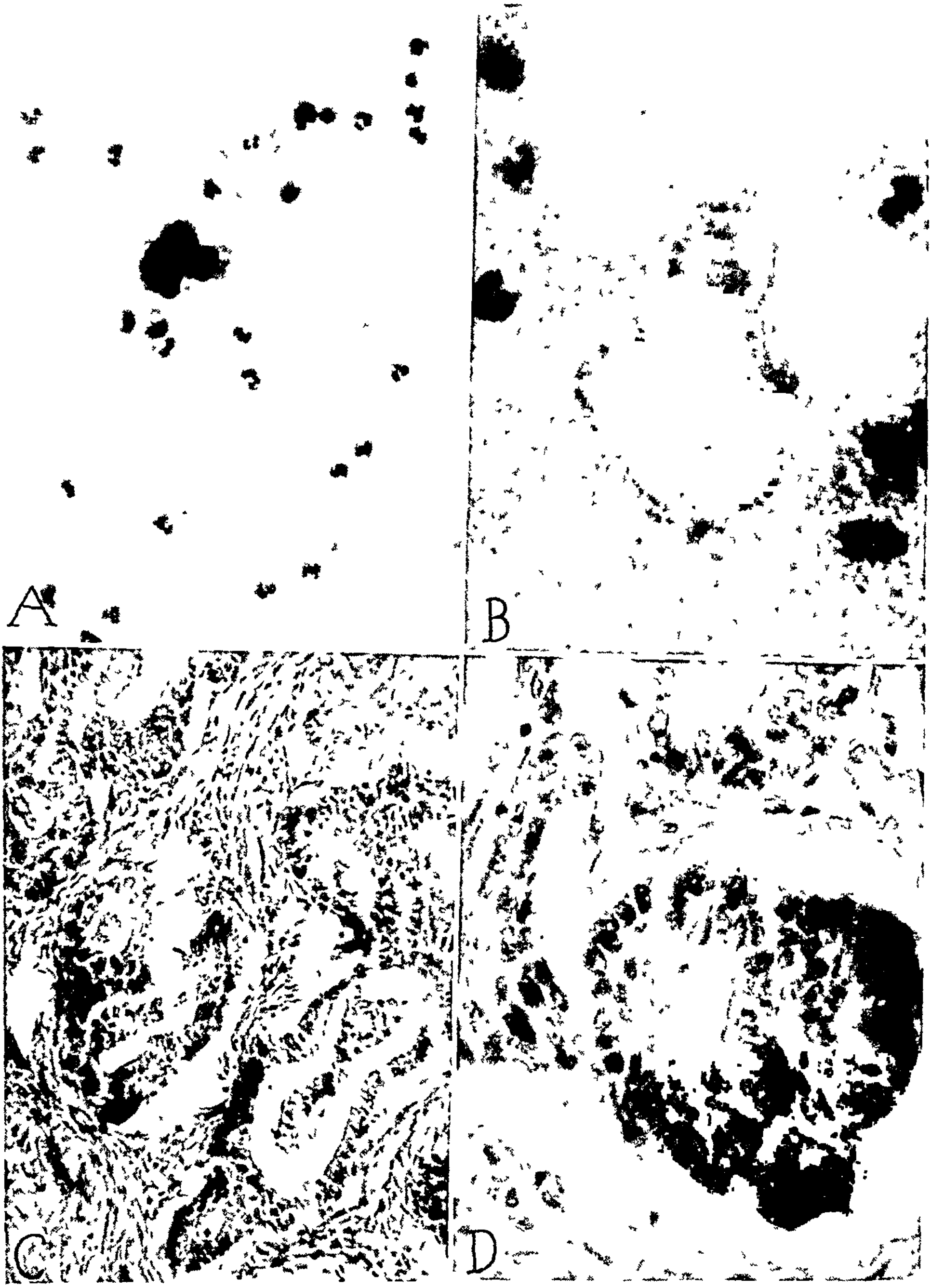

FIG. 3 *A*, cluster of three enlarged, overlapping, moderately hyperchromatic nuclei surrounded by leukocytes. *B*, high magnification of *A*. *C*, section of prostate gland which shows early tubular carcinoma. *D*, high magnification of C

definite malignant features and can be easily detected by screening. An early unsuspected case of bladder malignancy was detected cytologically in the urine sediment of a 70-year-old man who was free from any symptoms referable to the urogenital tract. Neoplastic cells were demonstrated in abundance on repeated

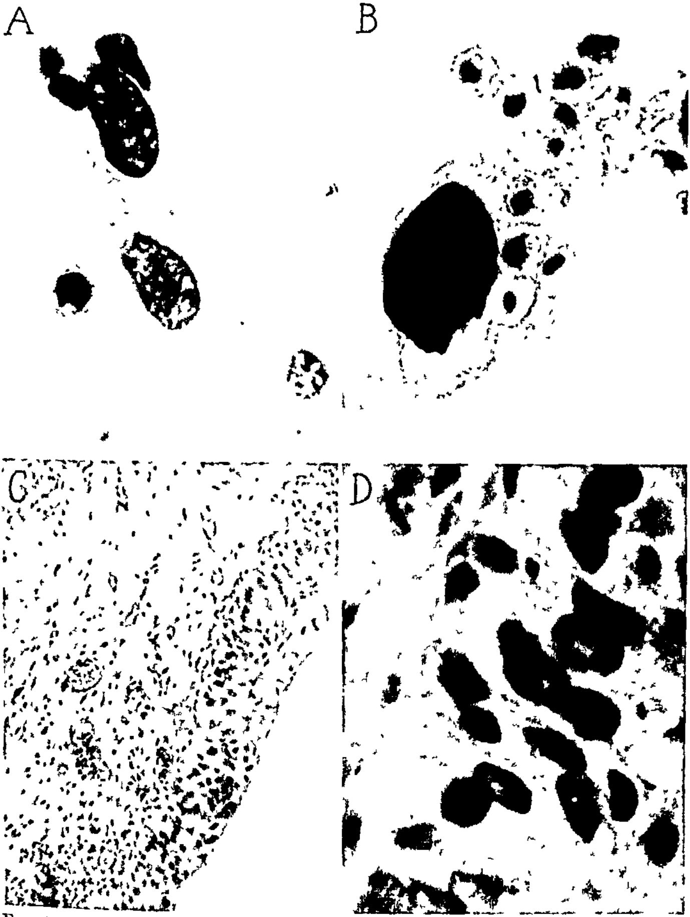

Fig. 4. *A*, several isolated malignant cells with large, irregular and hyperchromatic nuclei and prominent nucleoli. *B*, giant malignant cell exhibiting phagocytic activity. *C*, low magnification of section of bladder showing epidermoid carcinoma grade I. *D*, high magnification of *C*.

examinations of specimens (fig. 4, A and B). Cystoscopic examination revealed a small, benign-appearing papillary growth near the neck of the bladder. A biopsy of this lesion was reported as carcinoma in situ. The patient underwent transurethral resection of the growth and the postoperative report on the resected tissue was epidermoid carcinoma grade I (fig. 4, C and D).

SUMMARY AND CONCLUSIONS

A preliminary report is presented on the cytologic study of the prostatic secretion and urine sediment from 1,738 asymptomatic male patients 50 years of age and over. These patients were examined at the Strang Prevention Clinic, Memorial Center during a period of three years. Clinically suspicious cases were excluded from this study.

Two proven cases, an unsuspected grade I carcinoma of the bladder and a clinically unsuspected adenocarcinoma of the prostate were detected primarily by the cytologic method.

The cytologically suspicious and atypical cases in this group of patients have not been confirmed clinically or pathologically. The difficulty involved in proving the presence of a prostatic carcinoma based upon suspicious or positive cytologic findings without clinical evidence necessitates a long-term follow-up of these patients with careful clinical evaluation and repeated cytologic studies.

Further knowledge concerning the identification and significance of many of the unknown cells appearing in the prostatic secretion and in the urine after massage is now in the process of being obtained by restudy and re-evaluation of smears as well as the study of tissue sections from the various areas of the genito-urinary tract.

At the present time it can only be concluded that this project must be continued on a research basis for a number of years before its value can be accurately estimated in cancer detection clinics or in the physician's office.

This study was initiated by the late Joseph Scapier, M.D., Director of the Laboratory of Cytology, Strang Clinic.

The author wishes to thank Mr. Andrew Ricci for his technical assistance.

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CARCINOMA OF THE SEMINAL VESICLE: REPORT OF TWO CASES

BAXTER A. SMITH, JR.

It would seem that carcinoma of the seminal vesicle is neither as rare nor as hopeless as the sparce literature would infer. Three of the few papers (Brack,[1] McCrea,[2] Gee[3]) on the subject report two cases each.

Lazarus[4] reviewed in detail the 20 cases reported to 1946 but did not include the two cases of McCrea or that of Morales, et al.[5] Gee reported two cases in 1948 and Devos[6] reported a case in 1951. It would seem that 26 cases have been recorded though all may not have been primary vesicular carcinoma. Three of the patients were in their 30's. Melicow[7] mentioned the diagnosis in three instances, one of which apparently was surgical. Doss[8] has treated one case by prostatovesiculocystectomy.

PATHOLOGY

The tumors are usually surrounded by a rather firm capsule but frequently extend to involve the adjacent bladder and prostate; they tend to spread to the opposite vesicle but do not seem to implicate the rectum except by displacement. The tumor tissue frequently is described as yellowish, orange, or reddish brown. Microscopic appearance may be anaplastic but usually is papillary or acinar with columnar or cuboidal cells. Metastases occur in the regional nodes, liver, and lungs in that order. Several cases, including one of the author's, have a long story denying the general opinion of rapid progression. McCrea states that the tumors are of low grade and progress slowly.

SYMPTOMS

Hematuria, frequency, dysuria, and difficulty in voiding are the urological symptoms. Pain on ejaculation was recorded in Junker's[9] case. Hemospermia has not been noted. Pain in the perineum and groin is frequent. Frequency of stool may be present with rectal compression. Most of the cases recorded are those of autopsies and the complaints noted in the reports are frequently due to distant metastases.

Accepted for publication April 6, 1953

[1] Brack, E. Ueber primare Samenblasencarcinome unter Beibringungen zweier neuer Falle. Ztschr. Urol., 15: 232, 1921.

[2] McCrea, L. E. Primary carcinoma of seminal vesicles, report of two cases and review of the literature. Urol. & Cutan. Rev., 46: 700, 1942.

[3] Gee, E. M. Primary carcinoma of the seminal vesicle, report of two cases. Brit. J. Urol., 20: 72, 1948.

[4] Lazarus, J. A. Primary malignant tumors of the retrovesical region with special reference to malignant tumors of the seminal vesicles, report of a case of retrovesical sarcoma. J. Urol., 55: 190, 1946.

[5] Morales, L., Obrador Alcelde, S. and Perrin, T. G. Analecta Med., 4: 3, 1943.

[6] Devos, R. Adenocarcinome primatif de la vésicale séminale. J. Belge d'urol., 19: 301, 1951.

[7] Melicow, M. M. Bladder neoplasms. A review of over 2500 biopsies and specimens. Read at A.U.A., Atlantic City, June 26, 1952.

[8] Doss, A. K. Personal communication.

[9] Junker, Ein Fall von primarem Samenblasencarcinome. Ztsch. f. Urol., 35: 209, 1941.

FINDINGS

Rectal examination is naturally of prime importance and reveals a hard, nodular mass, sometimes described as pear-shaped, in the region of one of the vesicles. This may or may not be separable from the prostate. It is definitely extrarectal but may encroach upon the rectal lumen. Fixation is described even in the surgical cases but rectal examination under anesthesia is not specifically stated. Distention of the bladder may be present due to residual urine. Evidence of metastases may be present.

Cystoscopic examination, when done, has revealed a normal bladder and has revealed mucosal involvement of the bladder. The usual picture presented shows elevation of one side of the base of the bladder with upward displacement of the ureteral orifice and edema of the vesical mucosa overlying the extravesical mass. The source of hematuria usually is not found.

X-ray examination may show displacement of the base of the bladder and filling defect. Calcification was present in one of the author's cases. Vesiculography has not been done but would perhaps be of great help, particularly if made by vasostomy. In a suspected case (carcinoma in vesical diverticulum between vesicle and vas) displacement of the vas and a normal vesicle except for calcification were shown. Normal upper tract or ipsolateral obstruction may be revealed by pyelography.

BIOPSY

The diagnosis may be established by biopsy. Transvesical biopsy was done in the author's cases and if feasible would seem preferable. McCrea's attempt was not successful but he made the diagnosis in both his cases by biopsy per rectum. Perineal punch biopsy was mentioned by Melicow. Biopsy at abdominal exploration has been performed.

DIFFERENTIAL DIAGNOSIS

All tumors of the rectovesical area are suspect. Seminal vesiculitis and carcinoma of the prostate with extension to the seminal vesicles, sigmoid carcinoma or diverticulitis in a deep pouch of Douglas, Blumer's shelf, cyst of the seminal vesicle or müllerian duct, and rectovesical septum tumors (sarcoma, fibroma, and xanthoma) are the main problems. In a case of carcinoma in a diverticulum of the base of the bladder, the findings were almost typical of vesicular carcinoma. Echinococcus cyst in cul de sac would be a differential problem in areas where hydatid disease is endemic.

TREATMENT

Therapy depends upon the stage of the disease. In the two reported cases treated by other than palliative surgery, Junker performed vesiculectomy through an ischiorectal approach, and Schmidt, as reported by McNally and Cochems,[10] performed vesiculectomy by perineal route. Junker's patient was well 5 months after surgery when reported and Schmidt's patient was well 2 years after surgery.

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[10] McNally, A. and Cochems, F. M.: Primary carcinoma of the seminal vesicles. J. Urol., 36: 536, 1936.

Unless the lesion is definitely movable and encapsulated without any evidence of local extension, prostatovesiculocystectomy with lymphadenectomy should be preferable. Palliative treatment by x-radiation or radon has been used.

CASE REPORTS

Case 1. O. S., a carpenter aged 60 (University Hospital No 737380), was first seen in 1943 at the age of 55, complaining of the passage of yellowish semi-solid material in the urine and the feeling of nervous exhaustion, both symptoms of 18 months' duration. The patient stated that blood and yellowish, semi-solid, jello-like material were extruded upon massage. Occasionally, there was spontaneous passage of this material as well He had numerous complaints relative to his status of nervous exhaustion, including loss of libido.

The prostate was described as enlarged in the region of the right lobe Examination of the urine was normal. A smear of "vesicular secretion" contained many pus cells Cystoscopy was advised by the urological department.

The patient was next seen in September 1948. In 1945, he had received shock therapy. The patient complained of symptoms of prostatism of about 3 months' duration; questionable hematuria had occurred.

Examination was essentially the same. The prostate was slightly enlarged and benign with a *firm nodular mass above the right side of the prostate. It was two* to three centimeters in diameter. Examination of the urine was again negative The acid phosphatase was 2.3 King Armstrong units Excretory urogram was normal except for incomplete rotation of the left kidney. The diagnosis was thought to be a question of a rectal shelf or carcinoma of the prostate Cystoscopy was performed by Dr. B. J. McGroarty. There was rather marked collar type of prostatic hypertrophy. Midway between the vesical neck and the verumontanum was a large open duct about one centimeter in diameter which opened into a pocket which contained necrotic debris. This looked like either a dilated prostatic duct or ejaculatory duct. The ureteral orifices were normal There was trabeculation grade 2 of the bladder and the base of the bladder on the right was somewhat elevated Impression was benign prostatic hypertrophy with chronic right seminal vesiculitis A transurethral resection of 22 gm of benign prostatic tissue was performed After the prostate has been resected, the tract was laid open and much mucinous material and several bites of tissue were removed from the floor of the space. Rectal pressure caused much mucinous material to be expressed from the mass and it was thought that there was a probable cyst of the seminal vesicle.

Pathological report of tissue from the vesicle showed a rather dense fibrous stroma containing numerous mucinous secreting glands

The patient was readmitted on August 11, 1949 He stated that since his transurethral prostatectomy he had had perineal pain almost constantly and had passed "chunks" in the urine. He had no difficulty in voiding The physical findings were essentially unchanged Rectal examination revealed a tender, firm,

but not stony hard, golf ball sized mass, which felt slightly lo
at the base of the prostate and bladder and pressure upon the
the patient's pain. Examination of the urine revealed occasion
bacter aerogenes was present upon culture. The acid phospha
Armstrong units.

Cystoscopy was performed by Dr. M. J. Feeney. The right
meatus extending almost to the ureteral orifice was covered w
which appeared papillary at the periphery. This extended
static urethra for about a centimeter in the 7 o'clock posit
orifices were normal though the right orifice was displaced a
tumor. Biopsy with the resectoscope was performed and
cinoma.

On August 19, 1949, bowel preparation was begun; sulf
t.i.d., and on August 21, ½ gm. of dihydrostreptomycin, q6
night before surgery, the patient was given a sterile enema
sulfathaladine.

On August 23, prostatovesiculocystectomy was done car
fascia of Denonvilliers attached to the seminal vesicles and
modified Cordonnier ureterosigmoidostomy was done using
00 chromic catgut, mucosa to mucosa, suture to invert the
anastomosis. The short end of the suture was left about thre
and passed up the ureter as a quill. Other sutures of the ar
0000 chromic catgut.

Convalescence was smooth until the fourth postoperative

FIG. 1. Case 1. *A*, posterior view of specimen. *B*, opened bladd
(Negative was reversed during process of photography. In illustrat
on patient's left side whereas it actually was on right side, as stat

good until the sixth day. The night of the second postoperative day and the morning of the third, he was given three grams of sulfathaladine by mouth for a total of six doses. On the third postoperative day, blood urea nitrogen was 42 mg per cent.

On the sixth postoperative day, the patient was ill. Urinary output the preceding night had been only about 15 cc. Blood urea nitrogen was 72. The patient had abdominal tenderness, not localized. He was icteric. The abdomen was rather silent. Blood culture was taken and subsequently showed Aerobacter aerogenes.

It was believed that peritonitis was present and in the absence of localized findings, it was thought that one of the anastomoses had pulled loose, and that the peritoneum had been re-absorbing a good bit of urine and the patient hadn't become ill until the urine in the peritoneal cavity had become well infected. It was thought that this would explain the rising blood urea nitrogen with a good urinary output. Despite the patient's poor condition, bilateral cutaneous ureterostomy was performed with high caudal anesthesia. The left ureter was not dilated, the peritoneum was opened. Suction revealed no large quantity within the abdominal cavity. The right ureter was dilated to about three times normal size and an 18 Foley catheter was passed to the renal pelvis, about 15 cc of cloudy urine were present in the pelvis. This showed Aerogenes upon culture. The patient continued downhill with but little urinary output and expired the following day.

Microscopic pathology: "... Sections taken through the right seminal vesicle show large cystic spaces lined by poorly differentiated epithelium. The epithelium is arranged in single layers. Filling the cystic spaces is mucin. ... These cells appear relatively uniform in size. They are somewhat hyperchromatic. In some areas, the epithelium is piled up making a papillary appearance projecting into the cystic glandular spaces. Conclusion: Mucinous adenocarcinoma of the right seminal vesicle." C. W. Freeman.

Autopsy findings. Gross examination of the right kidney revealed acute pyelonephritis, and on microscopic examination of the kidney, colonies of bacteria were seen in the tubules. The stump of the right ureter was removed separately along with the adjacent colon. Probing from above revealed obstruction and grating. The ureter was split longitudinally into the bowel (fig. 2). Caliber of the ureter was adequate but the ureter was completely filled for a distance of about three centimeters upward from the meatus with impacted golden crystalline material. The mucosa was edematous and hemorrhagic. The catgut previously inserted was covered with the crystalline material also. Examination of the crystalline material scraped from the ureter showed a large number of crystals thought to be probable phosphates and a good number of crystals, which appeared to be microscopically typical of sulfonamide crystallization. The tablets in the sulfathaladine bottle, from which the patient received his dosage, were checked by Dr. Arnow of Sharp and Dohme and found to be sulfathaladine. Unfortunately, the catgut with the attached crystals, which was to be sent also, was inadvertently lost, so that analysis of the crystals by them was not feasible.

The course of events would indicate that crystalline obstruction occurred in

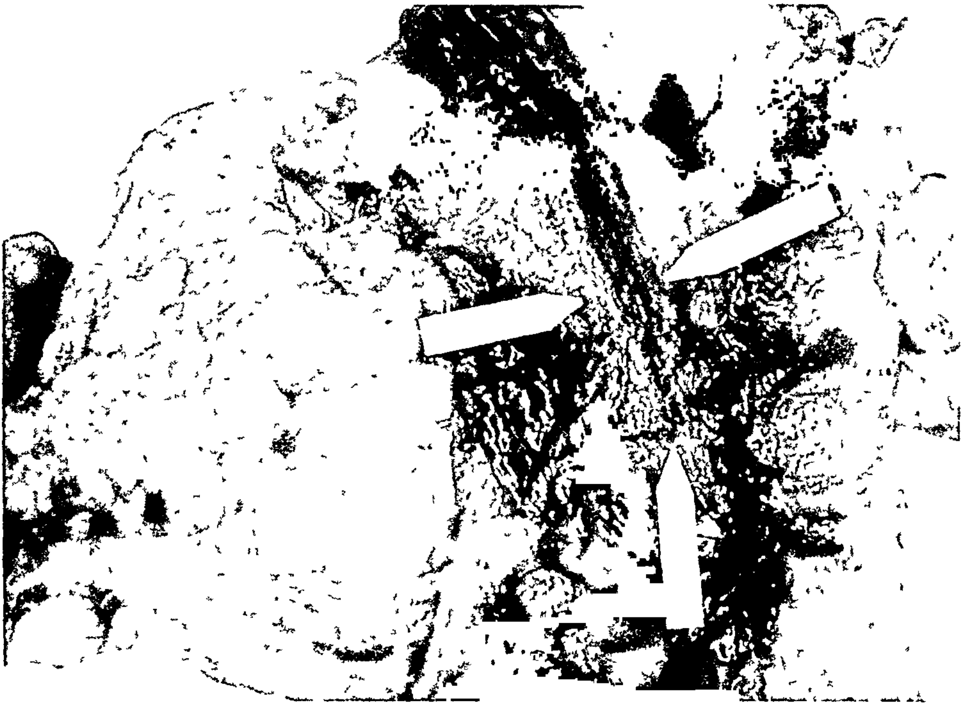

FIG 2 Case 1 Autopsy specimen of right ureteral anastomosis showing impaction of crystals in intramural ureter with hemorrhagic ureteritis above

the right ureter at and above the site of anastomosis with Aerobacter aerogenes pyelonephritis and septicemia. The latter was verified by a positive blood culture.

Case 2. E. C., a sheriff aged 66, (Abbott Hospital No. 149992), had a left pelviolithotomy in 1942. In July 1948, vasectomy and transurethral prostatectomy of 55 gm. of benign prostatic tissue were performed.

The patient was next seen on September 5, 1951, at the age of 66. He stated that he had had no complaints referable to voiding. In May 1951, he had hematuria which lasted for about a month. The hematuria was usually initial, but sometimes mixed. He had not noted any hematuria since that time and had been gaining weight. Examination of the urine was negative. Rectal examination revealed a firm to hard mass at and above the base of the prostate on the left. Only the lower portion of the mass could be palpated. It felt somewhat nodular and protruded into the rectum rather remarkably. The portion palpable seemed to be about four centimeters in diameter. Mobility could not be determined. His duties as sheriff again were pressing, but cystoscopy with cocaine anesthesia was undertaken. This was rather unsatisfactory because of deformity of the bladder and lack of relaxation, but the findings were similar to those of cystoscopy under anesthesia as outlined below. It was believed that the patient had extensive infiltrating carcinoma and hospitalization was advised.

The patient did not return for hospitalization, however, until October 2, 1951. He stated that he had had hematuria for about two weeks with varying urgency and frequency. The hematuria had again ceased, but impressed him sufficiently so that he recognized the advisability of medical care. Pain of an aggravating nature had developed in the left groin.

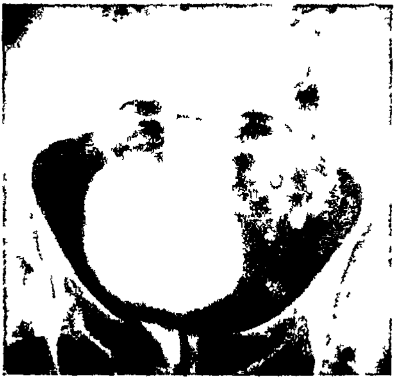

FIG 3 Case 2 Resultant cystogram of excretory urogram Note displacement of bladder and filling defect Appearance of bullous edema is recognizable in original film

Rectal findings were as before An excretory urogram revealed the upper tract to be normal with deformity of previous pelviolithotomy on the left There was a rather marked deformity of the bladder, which showed a large filling defect in the left side of the bladder, with edema of the mucosa overlying the filling defect (fig 3) The bladder was displaced toward the right

On October 4, 1951, cystoscopy was performed with a preoperative diagnosis of carcinoma of the bladder The posterior urethra showed good prostatic channel There was displacement of the bladder cavity to the right The ureteral orifices were not seen There was a large, round mass extending from the one o'clock position to about the six o'clock position at the internal meatus This extended up into the fundus of the bladder involving the entire right wall It was covered with edematous mucosa After several bites with the resectoscope into this mass, large quantities of brownish, grayish liquid material entered the bladder and the mass more or less collapsed The surface was resected out, so that in part the area was saucerized The remaining space was about the size of a lime and when the resectoscope was introduced into it, the space was lined with soft shaggy tissue, pink with a brownish cast and necrotic material and old blood clots The tissue appeared to be rather papillomatous in areas On rectal examination, the mass rather markedly decreased in bulk after evacuation and on bimanual examination, induration was palpable The mass appeared to be movable and unattached to the rectum

Microscopic pathology " The section through the tumor from the cavity shows it to be composed of numerous glands and broad sheets of epithelial cells These epithelial cells are uniform in size and are fairly well oriented with one another Mitotic figures are not infrequently found The glandular spaces appear to be secreting hyaline staining secretion Tissue shows a histologic picture best fitting a malignancy arising in the seminal vesicle Diagnosis Adenocarcinoma of the seminal vesicle " C W Freeman

On October 8, 1951, surgery was performed through a midline incision (fig

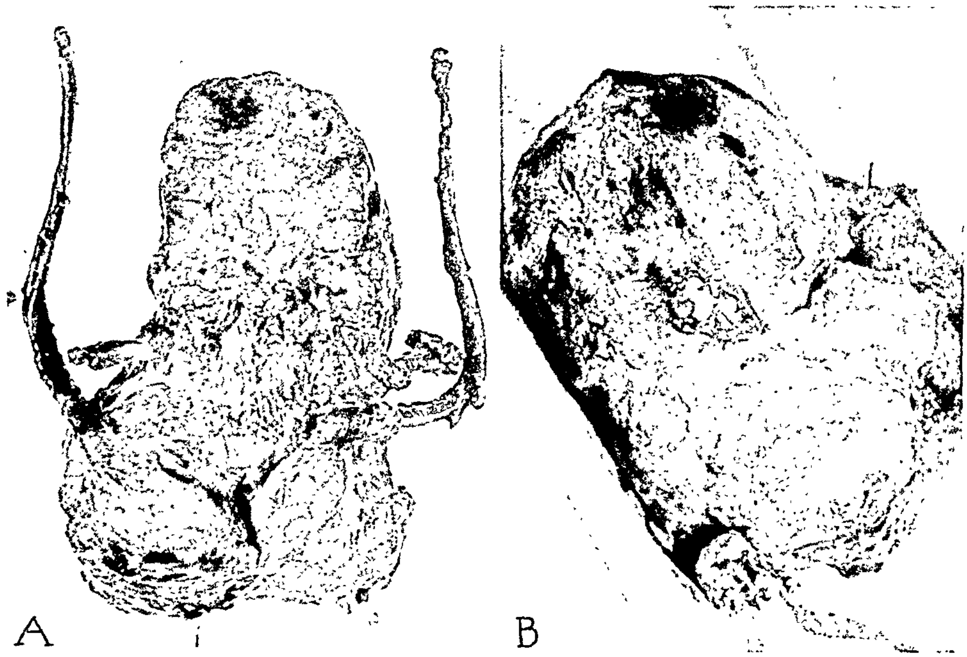

FIG. 4. Case 2. *A*, trimmed, distended specimen, posterior view. Coarse string ties urethra. Note Denonvilliers' fascia removed from right vesicle and incised over left vesicle. *B*, specimen from standpoint of rectal palpation, patient bent forward.

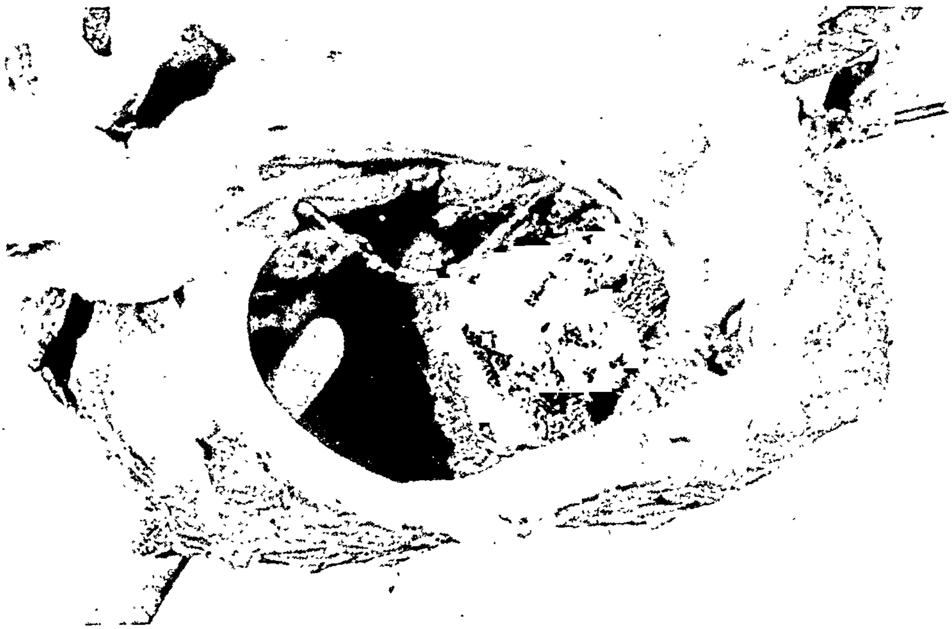

FIG. 5. Case 2. Interior view showing relationship of prostatic fossa, trigone and vesical involvement.

4). Lymphadenectomy was performed and prostatovesiculocystectomy was done, taking care to leave Denonvilliers' fascia intact. Ureters were implanted into the rectosigmoid. The space was counterdrained through the urethra with perineal urethrotomy and sharp incision of the triangular ligament (fig. 5).

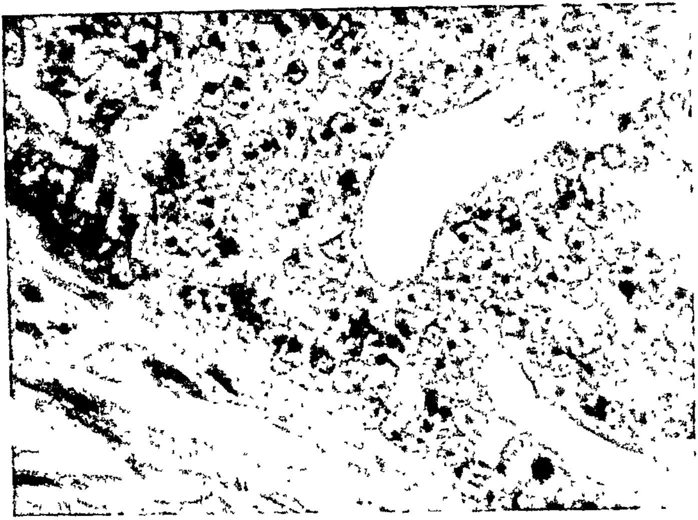

Fig. 6. Case 2. High power view of tumor showing alveolar arrangement of large pleomorphic cells.

Convalescence was smooth. The patient was discharged on the eighteenth postoperative day.

Microscopic pathology: "The sections through this tumor show it to be composed of poorly differentiated epithelial cells (fig. 6). These cells are in areas formed into glands. In other areas they appear to form papillary processes. The tumor invades the surrounding structure and in several sections is seen to invade the remaining prostatic tissue. The individual tumor cells are relatively uniform in size. They show occasional mitotic figures. The tumor cells appear fairly well oriented with one another. Cytologically speaking, the tumor does not appear extremely anaplastic. . . . Examination of the regional lymph nodes showed all twelve nodes on the right side to be uninvolved. Of 17 nodes from the left side, one node showed tumor identical with the primary tumor in the seminal vesicle. Of 2 nodes which were removed from around the bladder specimen, two were involved with tumor. . . . Diagnosis: Adenocarcinoma of the left seminal vesicle with metastasis to regional lymph nodes." C. W. Freeman.

The patient was last seen on March 26, 1953 at which time he felt well and no evidence of metastases or recurrence could be found. The right upper urinary tract was normal and the left showed dilatation grade 1 to 2.

DISCUSSION

In case 1, the passage of and finding of mucus, the palpation of the mass, and the cystoscopic findings made the diagnosis, confirmed by biopsy. With a history of seven years total duration, I suppose one might infer that a cyst of the seminal vesicle had undergone malignant degeneration. The diagnosis was made in case 2 when the vesicular space was entered with the resectoscope and proved by biopsy. I believe that the diagnosis may be made clinically rather accurately.

The history in case 1 extended over seven years and in case 2, five months intervened between onset of symptoms and institution of therapy. Histologic changes showed relatively low-grade malignancy albeit three nodes were positive in case 2.

The presence of sulfonamide crystals blocking anastomosis in case 1 seemed to be typical to microscopic examination and in view of Creevy's[11] previous experience, material was saved for differential sulfonamide chemical examination but was inadvertently lost. I am personally convinced that the insoluble sulfonamides should not be used in anticipated ureterointestinal anastomosis.

SUMMARY

Two cases of primary carcinoma of the seminal vesicles have been described in detail, bringing the reported cases to 28; at least four other cases have come to my attention.

It is believed that the lesion should be recognized clinically and may be proved by biopsy; cystoscopic if feasible, or perineal if the lesion is early, in which event local excision may be possible.

Prostatovesiculocystectomy would seem to be the logical and most thorough therapy from the standpoint of attempted cure.

The insoluble sulfonamides seem to be contra-indicated in anticipated ureterointestinal anastomosis.

ADDENDUM

The patient described in case 2 was well when seen April 14, 1951.

305 Medical Arts Bldg., Minneapolis, Minn.

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[11] Creevy, C. D.: Ureterosigmoidostomy and insoluble sulfanomides. Urologists' correspondence club, **16:** 58 (Dec. 13) 1949.

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TRUE HERMAPHRODITISM: A CONFERENCE ON THE MANAGEMENT OF ONE PATIENT

From the Department of Urology (James Buchanan Brady Foundation) and the Laboratory of Surgical Pathology of the New York Hospital, Cornell Medical Center, New York, N. Y.

DR. VICTOR F. MARSHALL (urologist): The subject of today's conference is a patient (N.Y.H. No. 161 213) with true hermaphroditism, that is, one with histological proof of both ovarian and testicular tissue. As only 50 such cases are recorded[1] and as the cases vary considerably among themselves, there is a scarcity of therapeutic precedents to guide us in the management of this patient.

DR. ALBERT J. PAQUIN (resident urologist): Eight years after the patient was born in this hospital, a repair of chordee, construction of a urethra from the perineal meatus with a skin graft and a left cryptorchiopexy were performed. At the age of 14 years both breasts began to enlarge and 10 months later a mass was noted in the left groin. On admission the patient was an apparent male of 15 years with enlarged breasts containing firm mammary tissue (fig. 1). The complexion was coarse but no definite beard was present. The pubic hair had a questionably feminine distribution. The pendulous portion of the penis was 6 cm. in length and of proportionate caliber. The right side of the scrotum contained a mass of 2 cm. diameter. A hard nodule of about 3 mm. in diameter was noted in the lower pole but the remainder felt like a prepubertal testis. Near the left pubic tubercle was a soft, nontender, ovoid mass of somewhat irregular outline and about 4 cm. in diameter. A small bilobed prostate was palpable rectally. Routine laboratory tests and an Aschheim-Zondek test were normal. The mass in the left groin was excised on the suspicion of testicular neoplasm.

DR. JOHN M. PEARCE (pathologist): A thin coiled tube 21 cm. in length and 1 cm. in diameter at its largest point was found filled with old blood. It was lined by atrophic endometrium and appeared like a lower uterine segment. A nearby site in the tube was lined with ciliated epithelium and appeared like an oviduct. An associated soft gray solid mass about three centimeters in diameter consisted of typically appearing ovarian stroma. Although ova were not present this appearance is so characteristic it seems reasonable to identify the structure as ovary.

DR. MARSHALL: The only true hermaphrodite previously found here had ovarian stroma without ova as the female gonadal tissue[2] (N.Y.H. No. 238 947).

DR. PAQUIN: An excretory urogram was negative but by cystourethrography an apparent vagina was noted. Endoscopically a 2–3 mm. aperture on the floor of the urethra, just internal to the verumontanum, could be entered as its sphincter-like tissue permitted easy dilation. Transverse rugae were evident and a small cervix at the inner end, about 9 cm. above, was seen. A hysterogram demonstrated a rudimentary uterine cavity deviated toward the left. The uri-

Accepted for publication July 20, 1953.

[1] Fischer, H. W., Lischer, C. E. and Byers, L. T.: True hermaphroditism. Ann. Surg., 136: 864–873, 1952.

[2] Stromme, W. B.: True hermaphroditism. Am. J. Obst. & Gynec., 55: 1060–1064, 1948.

nary 17-ketosteroid excretion in 24 hours was 5.6 mg. as measured here and 13.6 mg. as determined four days later by Dr. Kupperman.

Dr. Herbert S. Kupperman (endocrinologist at the New York University, Bellevue Medical Center): The normal range in our laboratory is 10–22 mg. per 24 hours for males and 8–18 mg. for females. Accordingly, differentiation of sex cannot be made by this patient's output.

Dr. Anne C. Carter (endocrinologist): In our laboratory the normal range is 8–14 mg. and at this patient's age 5.6 mg. would be normal for either sex. This child's creatinine index is 24, which is within normal for an adult male but would be elevated for an adult female. (The 24-hour creatinine output was 1.325 gm.).

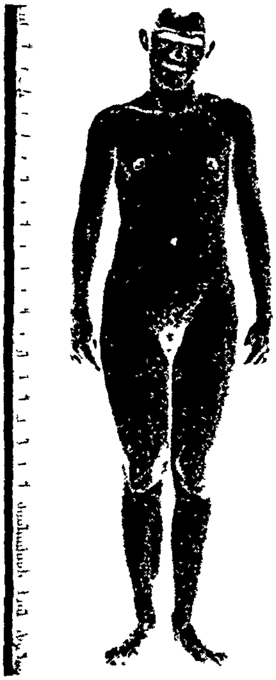

Fig. 1. General appearance shortly after exploration of left groin

Dr. Kupperman: Urinary gonadotrophic assay found 211 mouse units per 24 hours which is a marked and abnormal increase above the normal range of 6.6 to 52.8 for either sex at any age. On the same date an estrogenic assay found less than 5 mouse units (in fact too little to measure) in the 24 hour urine. This absence of estrogens could be considered normal for this age, for either sex. The development of the breasts in this case does not appear to be due to increased estrogenic activity but it should be remembered that the postpubertal mammary development of normal females is also associated with undetectable urinary estrogens. *One might conjecture here that the breast enlargement is similar to that in* Klinefelter's syndrome in which the absent or nonfunctioning Sertoli cells fail to produce inhibin. The facts concerning inhibin are by no means established but theoretically its lack permits pituitary hyperfunction including the increased elaboration of a mammatrophic factor. Patients with Klinefelter's syndrome do have relatively normal appearing Leydig cells.

DR. CARTER: Elevated gonadotrophins are present in Klinefelter's syndrome, prepubertal castrates, and our patient—and gynecomastia is present too. Actually the biological potency of circulating estrogens and androgens is unknown. The frequent gynecomastia of patients with liver disease seems due to failure of inactivation of estrogens, but no one has yet demonstrated a deviation of estrogen and androgen excretion.

DR. PAQUIN: The blood cholesterol was 153 mg. per cent; the cholesterol esters, 116 mg. per cent; and the per cent of ester, 71.9. A smear of sediment obtained endoscopically from the vagina revealed only superficial epithelial cells without cornification, which indicates an absence of estrogenic effect[3] and supports Dr. Kupperman's finding of no estrogens by urinary assay. Roentgenograms of the sella turcica were normal. X-ray pelvimetry demonstrated an android pelvis. The bone age, as reported by the radiologist using Todd's standards, was normal for a 15-year old male but more closely resembled that of a 13½-year old female. There was no significant premature closure of the epiphyses.

DR. CARTER: The glucose tolerance curve is somewhat flat but the insulin tolerance test was entirely normal. The 8-hour ACTH test produced a normal drop in eosinophiles.[4] Studies of the electrolytes including the salt withdrawal test found no evidence of electrolyte disturbance. (The patient was placed on a diet containing 1 gm. sodium and the 24-hour urinary sodium measured before and after the diet. A prompt and marked reduction indicated normal adrenal and renal function regarding this electrolyte.) The 17-ketosteroid excretion has been discussed. These particular studies provide no evidence of either abnormally increased or decreased adrenal or pituitary function but the increased urinary gonadotrophins do reveal that some part of the pituitary function is unusual.

DR. MARSHALL: The question of hyperfunctioning adrenals is important because nearly all genetic females with pseudohermaphroditism have either adrenal hyperplasia or actual neoplasm. The principal exceptions are those with arrhenoblastoma (and no hormonally functioning one has been recorded before puberty) and those with hyperfunctioning adrenal cortical tissue in a teratoma. At least one of the latter is in the literature and we have seen one infant male with virilism due to such tissue in a sacrococcygeal teratoma (N.Y.H. No. 622-766). If this 15-year old patient had adrenal hyperfunction, clinical precocity accompanied by elevated 17-ketosteroid excretion would be expected, but neither is present.

DR. KUPPERMAN: The increased gonadotrophic excretion from the pituitary would be inconsistent with a diagnosis of precocious sexual development due to excessive adrenocortical activity because that activity inhibits pituitary function. One can reasonably presume that the gonads of this patient are functioning hormonally at a very low level and are not producing usual quantities of steroidal hormones.

DR. PAQUIN: The right scrotal mass was found to be composed of two grossly distinct parts. The upper component which comprised about 80 per cent of the whole was soft, mottled and salmon pink. This was biopsied in two separate places. The mass at the lower pole was completely excised, there being a clear delineation between the soft, pink, upper portion and the hard, white, lower one. What might have been a deformed epididymis was biopsied but no vas could be identified.

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[3] Shorr, E. An evaluation of clinical applications of vaginal smear method. J. Mt. Sinai Hosp., 12: 667, 1945.

[4] Renold, A. E., Jenkins, D., Forsham, P. H. and Thorn, G. W. Intravenous ACTH, a study in quantitative adrenocortical stimulation. J. Clin. Endocrin. & Metab., 12: 763, 1952.

DR. PEARCE: The hard, white mass is normal ovarian stroma with not only ova but also Graafian follicles in various stages of development. At least one corpus luteum was present. A glance at the sections from the biopsies of the larger component of the right scrotal mass shows testicular tissue. The tubules are numerous, of approximately normal size, but are largely lined by Sertoli cells. Spermatogenic cells are extremely rare and no spermatozoa or heads of spermatids could be found. The interstitial fibrous tissue seems unremarkable but the Leydig cells seem more abundant than in the testis of a normal 15-year old boy. The suspected epididymis was only fat and blood vessels. Thus the right scrotal mass is a so-called ovotestis.

DR. MARSHALL: Having read the operative note about the left orchiopexy I wonder whether the left gonad might not also have been an ovotestis, with only ovarian stroma remaining now.

In summary, the patient has the following feminine characteristics: an ovary on each side with one ovulating; a vagina; a cervix; a uterus; at least one fallopian tube; developing breasts bilaterally and suggestively feminine distribution of hair. On the masculine side are: a testis with Leydig cells; normal sized tubules and Sertoli cells (but no spermatozoa); a distinctly masculine phallus, even before the plastic operation; a palpable prostate; a well developed scrotum containing gonads; a masculine habitus; no evidence of estrogenic activity by urinary assay or examination of the vaginal smear and finally, a mental orientation decidedly masculine. Endocrinologically there is no clear indication of the predominant sex but there is endocrine activity present and this activity is unusual. This sexually abnormal patient must live in a society not tolerant of such aberrations. He must live with himself and he already has conflicts between his previously supposed masculine status and his physical evidences of femininity now, the breasts particularly.

DR. DONALD GREAVES (resident psychiatrist): We all assume that normals, pseudohermaphrodites and even true hermaphrodites have a predominant sexual orientation. As far as I know all true hermaphrodites have had a psychologically predominent sex. Certainly this patient is psychologically masculine. This opinion is based mainly on a thorough personality study of a type which I think should be carried out in any hermaphrodite. The first item to consider is the patient's appearance and behavior. On admission he was described as a male and had been admitted to a ward for males. He looks, acts and gestures like a boy. He seems to have some change in voice. His behavior about the distinctly feminine breasts is especially impressive, he hides them as any self-respecting boy might be expected to do. Secondly, the patient's interests, strivings and

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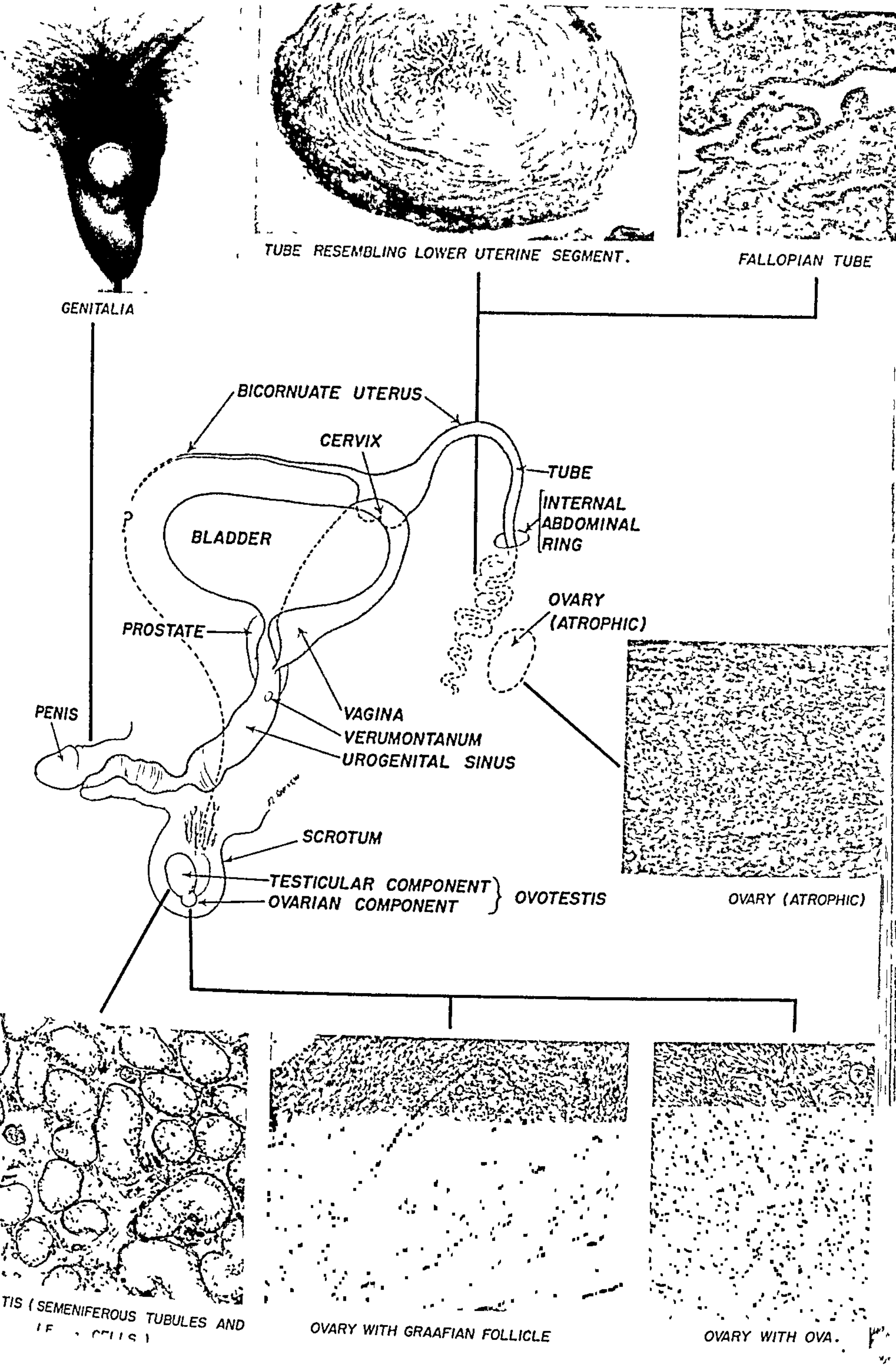
FIG. 2 (See facing page).


GENITALIA
TUBE RESEMBLING LOWER UTERINE SEGMENT.
FALLOPIAN TUBE
BICORNUATE UTERUS
CERVIX
TUBE
INTERNAL ABDOMINAL RING
?
BLADDER
OVARY (ATROPHIC)
PROSTATE
PENIS
VAGINA
VERUMONTANUM
UROGENITAL SINUS
SCROTUM
TESTICULAR COMPONENT
OVARIAN COMPONENT
OVOTESTIS
OVARY (ATROPHIC)
TIS (SEMENIFEROUS TUBULES AND
CELLS)
OVARY WITH GRAAFIAN FOLLICLE
OVARY WITH OVA.

goals are to be noted. He likes football, not sewing; fishing, not cooking; etc. He wants to be and considers himself to be like his father, not his mother. He has a special girl friend in school, not a special boy friend. Thirdly, the personality traits and patterns of thought must be considered. While this may sound vague we are all familiar with what we call masculine and feminine traits and thought patterns (think of all the jokes based on this realization). The patient seems to me to be more assertive like a well-behaved boy than retiring like a well-behaved girl. He is certainly more forthright in his response to me than coquettish, for example. Although too lengthy to describe here, he talked to me as if I were a person of the same sex he considered himself to be and this is a particularly valuable notation before puberty. After puberty there are additional factors to be evaluated: the general sexual functioning, the nature of the sexual desire and sexual fantasies, the performances and feelings of the patient about these matters. The fourth and possibly most important consideration is the patient's background and raising. Has he been reared as a girl or boy? The evidence in this case is conclusively on the masculine side. Finally, there are some psychological tests which might be of help in certain cases. In brief, the basic items have been: appearance; behavior; interests; goals; personality traits and raising.

DR. MARSHALL: Would you guess how much of this orientation is due to heredity and how much to environment? As far as I am aware all true hermaphrodites have been mentally orientated in the sex in which they have been raised, except for the one previous case studied here (a detailed psychiatric evaluation was not made, however).

DR. GREAVES: Psychiatry has shown how important a role upbringing and environment may play in producing sexual deviations in individuals who, according to all present investigative techniques, are biologically and hormonally normal. While I have listed the significant psychological factors in his rearing and environment which have oriented him as a boy, I cannot underestimate the importance of his having been born with an apparent penis. I cannot determine accurately the effects of his hormonal factors, which in themselves are poorly understood, on his appearance, behavior etc. On the basis of experience with sexually deviated persons with no known biological abnormalities, I believe that the upbringing is of predominant importance. This patient, for example, is far more masculine in sexual orientation than one would expect from his biological construction. Therefore, while I cannot quantitatively answer your question I do think that the environmental factors have been of greater effect on this patient's orientation than the biological factors.

DR. MARSHALL: The patient is anatomically and probably endocrinologically both male and female, yet psychologically he is established as a male. Parenthood in either sexual capacity is excluded. No autoconceptions have ever been proved (one true hermaphrodite described in the literature had semen containing sperm and histologically functioning ovaries but even this is a long way from self-impregnation). Our patient has no vas and no true sperm. The ovulating tissue has now been removed but if it remained impregnation via this vagina, uterus and oviduct would seem nearly impossible. Let us briefly consider making this patient more feminine.

Dr. Paquin: This would involve: conservation of ovarian tissue (not now possible), amputation of the penis, removal of testis, forming the scrotum into a vulva and bringing the vagina down to the vulva (this last has been done by the late Dr Hugh Young,[6] C. D. Creevy and others).

Dr Carter: Estrogens would probably produce fuller breast development. Intermittent therapy with estrogens or estrogens and progesterone would cause withdrawal bleeding if the endometrium is capable of responding to these hormones

Dr. Greaves: The patient would then be a menstruating boy with breasts, not a girl. Effecting a change in the psychosexual orientation of this patient would be vastly more difficult than the surgical problem

Dr. Paquin: The very clear psychological indication to increase the masculinity in this case seems determinative. Although there are other factors favorable to masculinity as well, these could be apparently overcome without excessive effort The remaining gonad is in the scrotum, contains Leydig and Sertoli cells and does not evidence estrogenic activity (the gynecomastia being accounted for on other grounds at least theoretically).

Dr Marshall: This testis is not normal histologically and conceivably may be, or might become, abnormal hormonally. At least six of the patients recorded by Dr H. H. Young with true hermaphroditism menstruated between 15 and 30 years of age. The vaginal smears and urinary estrogenic assays could be followed for evidences of estrogenic activity. Actually the urinary sediment after a prostatovaginal massage would likely provide good evidence of estrogenic activity. Dr. Papanicolaou usually reports correctly when a male is receiving estrogen on the basis of the changed appearance of cells from the posterior urethra. I believe we should leave this testis in place. A plastic removal of breast tissue is indicated, not only by psychological reasons but also to obviate further development under any circumstances.

Dr. Richard Stark (plastic surgeon): Furthermore, the result would be prompt and fulfill the patient's chief desire. Drs. George V. and Jerome P. Webster have developed a semicircular approach around the inferior hemicircumference of the areola through which the entire mammary tissue and fat can be removed en masse or piecemeal. Bleeding is controlled mainly by pressure but occasionally needle aspiration is needed postoperatively. The scar is barely discernible. Would administration of androgens be likely to reduce these breasts? He might require androgen later for other reasons, perhaps.

Dr Carter: No. Androgens, especially methyl testosterone but also testosterone propionate, can produce gynecomastia

Dr Marshall: Before leaving the cosmetic field a testicular prosthesis should be considered—only on the left where there is no mass and where no desirable structure would be interfered with. At this time a permanent artificial testis would not likely be ideal regarding size for both the present and the future. Although fat, rib cartilege etc. could be used the more permanent for size, shape and consistency would probably be made of foreign material such as vitallium, tantalum or plastic. Weight is also a consideration. An ovoid mass of tantalum mesh seems worth considering. Incidentally, I do not believe the testis portion of an ovotestis has been permitted to remain before but it was anatomically feasible in this case. One previous attempt resulted in leaving ovarian, rather *than testicular tissue, and further feminine development took place.*[6] Dr. Greaves, do you favor a prosthesis?

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[6] Young, H H Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases Baltimore Williams and Wilkins, 1937

Dr. Greaves: This patient now is well integrated and stable so the psychiatric hazard of the omission would surely be small.

Dr. Paquin: One cosmetic item not mentioned is the ability to void in the standing position. This patient can already do so because of his earlier plastic surgery. The present status of the penis also seems to indicate it will be useful for sexual intercourse.

A laparotomy is indicated. Third gonads are very rare but this case is rare too. Certainly any ovarian tissue should be removed. Adrenal enlargement is nearly excluded but the additional data from palpation would be of some academic value. The status of the internal genitalia would be better known and a hysterectomy to preclude menstruation under any later circumstances seems in order. The vagina would not be removed with the same ease as the uterus and furthermore vaginectomy seems unnecessary as the vagina alone cannot menstruate or produce any known hormones.

Dr. Marshall: We have several hypospadiac males with well developed vaginas but no difficulties have arisen in their regard, after construction of the urethras. At least one of these patients has had a bilateral biopsy to prove testes. This vagina does not empty and fill with urination and it could be removed later if necessary. Although there are no reports in the literature indicating damage to the urinary sphincter mechanism or fistula formation by vaginectomy in these cases, such does seem possible. Cecil[7] has called attention to the probably great frequency of vaginas in cases of marked hypospadias and suggested that many have passed unknown in years gone by without complications forcing their recognition.

Substitution therapy with testosterone might depress the remaining testis and thus far his development does not call for therapy of this type. In addition to avoiding confusion I see nothing detrimental in merely following him for the present.

Dr. Carter: May I bring up the point that early determination of sex in questionable cases is highly desirable, particularly in pseudohermaphroditism? Dr. Greaves obviously agrees strongly. We have had patients, raised as boys, surgically explored without a biopsy but subsequently demonstrated to have ovaries. At fifteen they were girls but raised as boys—and the reverse has oc-

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[6] Engle, E. T., Yeaw, R. C. and Lattimer, J. K.: True hermaphroditism: Supplementary report of case. J. Urol., **56:** 731–736, 1946.

[7] Cecil, A. B.: Surgical management of vagina in male construction in hermaphrodites. J. Urol., **62:** 709–712, 1949.

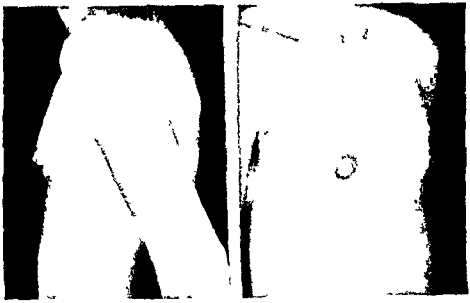

FIG 3 (Left), breasts before excision of mammary tissue (Right), breasts after excision of mammary tissue.

curred. Had the left gonad of this patient been biopsied at the time of the orchiopexy, a point at which the operative note proves the situation was not clear, this whole problem would have come to light then and some of the present problems avoided.

DR MARSHALL: Probably we should be less inhibited about biopsy of gonads, especially in cases of fairly marked genital anomalies. At what age level does it become difficult to change the psychological sex? Presumably it can be changed "early", but what is "early"?

DR. GREAVES: In the individual case the evaluation would have to be organized about four major items: first, the external appearance of the genitalia; second, the way in which the child has been raised up to the time of consultation; third, the speech productions and fourth, the behavior, mannerisms and habits. Also the attitude of the family is important as their aid is essential. Obviously the family can adjust better, the younger the child. Certainly before two years children are relatively undifferentiated. They do not converse and they behave nearly the same, so the appearance of the external genitalia and the way in which the infant has been raised are about all there is to go on. Between two and four talking begins. They are more interested in eating and elimination than in their genitalia but they do begin to see themselves, largely as a learned response, as either boys or girls. By the age of four children usually have a self concept as either boy or girl. This depends more on learned factors than on anatomical structure For example, boys begin to go with Dad or alone to the men's room rather than with Mommie to the girls' room. Such varied bombardments do not take long to impress the idea of being either a boy or a girl. I think that before the age of four decisions in questionable situations could be based on purely anatomical grounds (including biopsies etc.) and consultation with the family. Some psychiatric guidance might occasionally be needed, for the family at least. After the age of four a psychological switch to the opposite sex would, in usually expected circumstances, be extremely difficult and perhaps not ever completely successful From my point of view today's patient *is* a boy and we cannot change him into a boy (or a real girl) What we aim to do is to emphasize, support and reinforce what is masculine in him and minimize his feminine components and his anxieties about them.

Dr. Marshall: I believe we have indicated most of the problems in this case and made some reasonable decisions about therapy. Much of this material would seem applicable in other cases of hermaphroditism.

Follow-up note: The internal genitalia were found to be completely extraperitoneal. The tapering uterus was totally removed and the upper end of the vagina closed. The adrenals were not palpable and no additional gonadal tissue was discovered. The plastic operation on the breasts was carried out at the same time with an excellent result (fig. 3). Six months after the excision of the last known ovarian tissue the 17-ketosteroid output in the 24-hour urine was 3.04 mg. (and the creatinine .825 gm.) as found in the laboratory of Dr. E. Shorr here; and 1 month later, was found by Dr. Kupperman to be 6.7 mg. Seven months after the last excision of gonadal tissue there was no detectable estrogenic activity in the urine. Axillary hair and deepening of the voice appeared as did frequent erections (without ejaculations). Both the patient and his family are pleased with the results.

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THE EFFECT OF GANTRISIN ON PROTHROMBIN ACTIVITY

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A review of the literature indicates that alterations in the hematopoietic system have been associated with Gantrisin (sulfisoxazole) administration in 23 patients.[1-8] Agranulocytosis was reported in 3 patients, leukopenia in twelve, and hypoprothrombinemia in eight. In a recent study[9] of the undesirable effects of Gantrisin therapy in 23,000 patients no evidence of bone marrow depression was observed and there were no examples of bleeding tendencies associated with the use of Gantrisin. In this large group of patients, however, prothrombin activity as such was not determined unless there was some other indication for the procedure. Since one of the most frequent uses of Gantrisin is for pre- and postoperative prophylaxis, it was felt that a careful evaluation of the influence of this sulfonamide on prothrombin activity was indicated.

METHODS OF STUDY

Fifteen patients were selected at random from the Contagious Disease and Psychiatric Services at the Jefferson Davis Hospital. None of the patients was receiving vitamin K. A pretreatment prothrombin determination was performed in each case on May 1 and the administration of Gantrisin was begun in every case on May 2, 1953. Gantrisin was administered in doses of 1 gm. every 4 hours for the period of the study. The prothrombin activity was determined according to the method of Quick[10] twice weekly throughout the period of therapy.

RESULTS

The results of the study are presented in table 1. The prothrombin activity, as determined during the course of therapy, did not vary significantly from the pretreatment control determinations. Although the present group of patients was small, the lack of change in prothrombin activity added to the much more extensive clinical experience of absence of bleeding tendencies as observed in 23,000 patients would seem to be sufficient evidence that the administration of Gantrisin is very rarely associated with significant reductions in prothrombin formation. One patient being treated for actinomycosis showed no change in prothrombin activity after four months of Gantrisin therapy.

Accepted for publication July 29, 1953.

[1] Sarnoff, S. J.: Proc. Soc. Exper. Biol. & Med., 68: 23-26, 1948.

[2] Lazarus, J. A. and Schwarz, L. H.: J. Urol. 61: 649-657, 1949.

[3] [illegible] 62: 892-899, 1949.

[4] [illegible] 43: 868-871, 1950.

[5] [illegible] D. and Graham, C. M.: J.A.M.A., 144: 1179-1181, 1950.

[6] Gale, G.: Canad. Med. Assn. J., 64: 252-253, 1951.

[7] Hagerman, D. D., and Franzblau, S. A.: J.A.M.A., 147: 1657, 1951.

[8] Geiger, J.: J.A.M.A., 149: 1219, 1952.

[9] Yow, E. M.: Am. Pract. and Digest of Treat. In press.

[10] Quick, A. J.: Am. J. Clin. Path., 10: 222, 1940.

TABLE 1. *Effect of Gantrisin (1 gm. q. 4 hrs. begun May 2, 1953) on prothrombin activity*

CASE	5/1/53	5/5/53	5/8/53	5/12/53	5/15/53	5/19/53	5/22/53	5/26/53
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
B. T.	72	73	90	81	89	97	94	86
H. P.	79	71	86	92	79			
G. T.	69	67	90	81	83		92	90
C. H.	75	71	83					
S. O.	70	65	81	85	85	89	92	86
H. L.	76	71	84	74	83		83	82
L. G.	67	62	77	72	73		75	
H. W.	67	55	79	64	72	75	72	69
S. B.	78	76	95					
J. S.	76	84		85	97			
F. B.	80	80	77	94	85			
J. M.	80	84	81	100	100	91	94	
D. C.	80	94	92	97	93			
M. F.	78	94	81		97			
J. H.	78	84	81	85		83	85	
Average...	75.0	75.4	84.1	84.2	86.3	87.0	85.9	82.6

SUMMARY

The administration of Gantrisin (sulfisoxazole) in doses of 1 gm. every 4 hours produced no significant alterations in the prothrombin activity of 2 patients treated for 1 week, 5 patients treated for 2 weeks and 8 patients treated for 3 to 3½ weeks.

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AN INCISING ELECTRODE FOR USE WITH STERN-McCARTHY ELECTROTOME

WALTER M. KEARNS

The incising electrode here described (figs. 1, 2 and 3) is essentially a modification of the standard loop electrode which is transformed into a hooked beak formation. It is made in sizes to fit the variously calibrated resectoscopes.

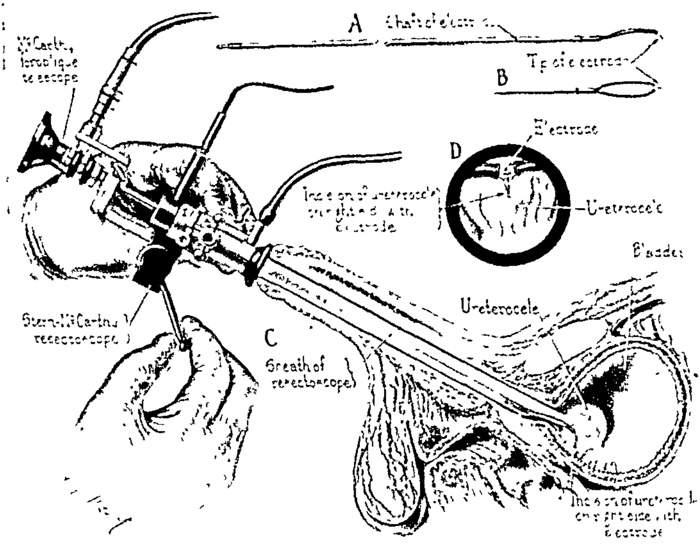
McCarthy foroblique telescope
A
Shaft of electrode
Tip of electrode
B
Electrode
D
Incision of ureterocele straightened with electrode
Ureterocele
Bladder
Ureterocele
Stern-McCarthy resectoscope
C
Sheath of resectoscope
Incision of ureterocele on right side with electrode

FIG. 1

It has been in use for more than four years and has been proven to possess some advantages over other types of electrodes because it allows better visibility of the contact of the active point of the electrode with the tissue at all times. In operation the electrode may be manipulated with the lever or button controlling its excursion in the working unit, or with the electrode held still in the sheath. Any combination of rotating, to and fro or side motion may be applied by movement of the sheath. An incision of any length in any direction and of any desired depth may be carried out to a nicety with the incising point constantly in view. Bleeding vessels may be accurately stopped with a minimum of destructive coagulation.

Read in author's absence by Dr. S. J. Silbar at annual meeting of North Central Section, American Urological Association. Grand Rapids, Michigan, October 6-9 1949.

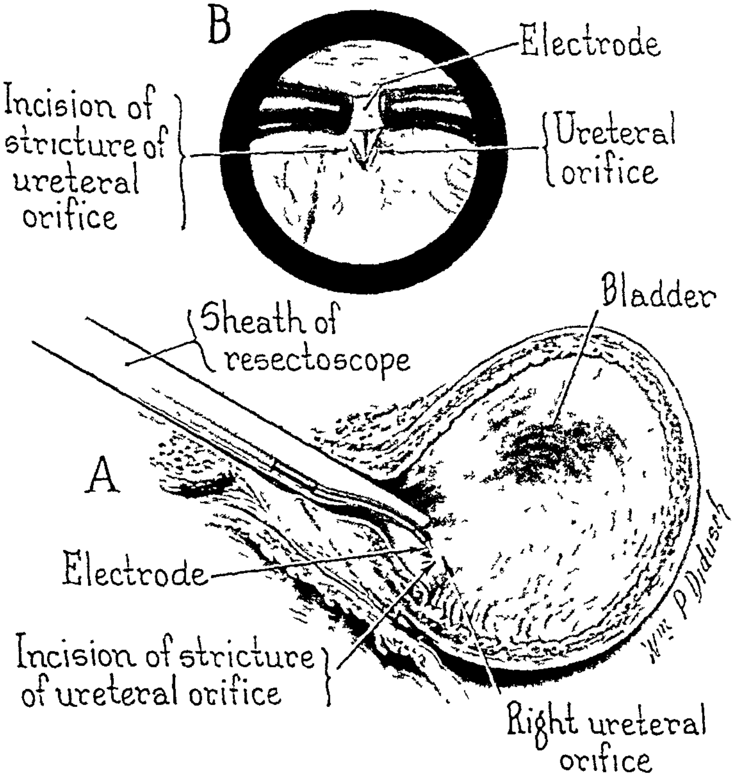
B
Electrode
Incision of stricture of ureteral orifice
Ureteral orifice
Bladder
Sheath of resectoscope
A
Electrode
Incision of stricture of ureteral orifice
Right ureteral orifice
Wm. P. Didusch

FIG. 2

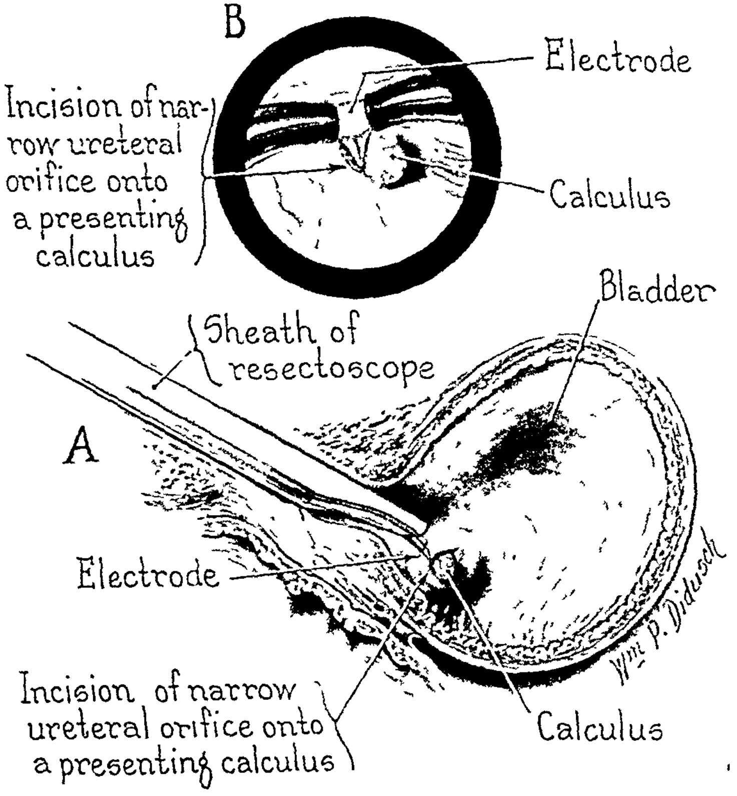
B
Electrode
Incision of narrow ureteral orifice onto a presenting calculus
Calculus
Bladder
Sheath of resectoscope
A
Electrode
Incision of narrow ureteral orifice onto a presenting calculus
Calculus
Wm. P. Didusch

FIG. 3

Its most common use has been in ureteral meatotomy to facilitate the passage of lower ureteral stones. Incision of ureterocele is accomplished with accuracy and minimal destruction of tissue. Cystic papillary formations at the vesical neck are readily eradicated. Through the smaller resectoscopes urethral strictures may be incised with single or multiple incisions.

The author wishes to express his thanks to Mr William P. Didusch and to Mr Frederick J. Wallace

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EXPERIMENTAL UROLITHIASIS VII: ROLE OF SEX AND GENETIC STRAIN IN DETERMINING CHEMICAL COMPOSITION OF STONES IN RATS

C. W. VERMEULEN* AND R. GOETZ

From the Department of Surgery, University of Illinois College of Medicine, Chicago, Ill.

In previous papers[1-5] of this series it has been indicated that if a foreign body be placed in the bladder of the rat, the foreign body serves as a nucleus about which a stone is formed, and that the stone so formed is composed of magnesium ammonium phosphate. The rats used in the experiments thus far reported were adult male albino laboratory rats obtained from a single source, the Harlan Small Animal Industry. More recently, by using rats obtained from a different breeder (Holtzman Rat Company) it was discovered that stones composed of calcium phosphates are produced instead of "magnesium" stones even though the animals were maintained on the same standard diet and under identical conditions. Because of this curious and unexplained difference in stone composition, a more extensive study was made in which the chemical type of stone was compared not only in the two different strains of rats but also in both sexes of each strain.

METHODS

Male and female adult white rats were obtained from the two breeders previously mentioned. A total of 10 males and 30 females of the Harlan strain and 52 males and 50 females of the Holtzman strain were used to obtain the data given in this paper. A foreign body was inserted in the bladder of each of these animals by means of a suprapubic cystotomy. The foreign bodies consisted of discs 4 mm. in diameter which were punched from a sheet of zinc. In the past it had been found that not infrequently a female rat was able to expell a foreign body of this size from the bladder; or, more commonly, the foreign body became impacted in the urethra leading to death of the animal. To avoid this possibility it was necessary to somewhat modify our customary operative procedure for foreign body implantation because both male and female rats were to be

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used in the present study. The foreign bodies were therefore suspended in the bladder on a loose loop of suture material passed through a small hole in the center of the foreign body. Since the loop was attached to the fundus of the bladder, the foreign body was effectively prevented from passing or becoming impacted in the bladder neck. Though this method is not needed for male animals, it was used for both sexes in the interests of experimental strictness.

The usual standard diet, Fox Chow checkers, was used for all animals. Drinking water was available to the animals at all times. Six weeks after foreign body implantation most of the rats were sacrificed. A few rats were allowed to go for longer periods in order to grow larger stones and give more material for chemical analysis. At the time of sacrifice the bladder was exposed and aspirated by sterile needle and syringe for urine culture and pH determination. The stone, if present, was then removed, dried, weighed, and analysed for calcium, magnesium, and phosphorus by the methods that have been described in previous papers.

During the course of the experiment some animals were placed in metabolism cages and urine from individual rats was collected for quantitative analysis for calcium, magnesium, phosphorus, and ammonia. Urine collections were made into flasks containing sufficient hydrochloric acid to prevent bacterial action. The urine from each rat was collected for 3 periods of 24 hours each. The 3 collections were then pooled and analysis run on the pooled urine. The analyses for urinary ammonia were done separately on individual 24 hour urine collections.

After the data had been obtained from this experiment, it became evident that the chemical composition of the stones was significantly influenced by the sex of the rat, and therefore an experiment was added to determine the effect of castration. Twenty adult male rats of the Holtzman strain were castrated in a preliminary operation four weeks prior to foreign body implantation. Subsequent treatment of these animals was the same as with those mentioned previously.

RESULTS

No statistically significant difference was found in the average weight of stone produced in the different groups of rats. In six weeks an average of 30–50 mg. of stone was formed by each group (after subtracting the initial weight of the foreign body). The average urinary pH likewise was the same in the different groups. Since this paper is primarily concerned with the chemical composition of the stones, details on the size of the stones in the different groups have been omitted.

The results of the chemical analysis of the calculi, as given in table 1 and figure 1, include all animals in which stones developed in a urine proved to be sterile on culture at the termination of the experiment. Some stones, however, were omitted because their small size precluded satisfactory quantitative analysis. Stones obtained from animals where a positive urine culture was obtained have not been included so as to avoid the possibility that accidental infection might have influenced the chemical composition of the stone. The table and

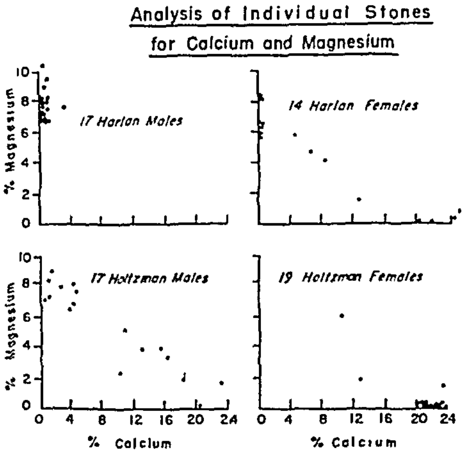

FIG. 1. Scatter graphs showing per cent of magnesium (ordinate) and calcium (abscissa) of male and female rats obtained from two different breeders (Harlan and Holtzman). Harlan male rats produce stones of almost pure magnesium ammonium phosphate, Holtzman females produce stones composed of a calcium phosphate salt, while remaining two groups form stones of varying composition.

figure indicate that the seventeen analysed stones obtained from the Harlan male animals invariably contained little or no calcium while the average magnesium content, 7.9 per cent, indicates that they are composed of almost pure magnesium ammonium phosphate hexahydrate (Mg content of this salt 9.9 per cent). *At the other extreme, the 19 analyzed stones from the Holtzman* female animals consisted almost entirely of a calcium phosphate salt containing

TABLE 1. *Chemical analysis of stones**

	NUMBER OF STONES ANALYSED	% OF STONE AS CALCIUM (AVERAGE)	% OF STONE AS MAGNESIUM (AVERAGE)	% OF STONE AS PHOSPHORUS (AVERAGE)
Harlan				
Male	17	0.6	7.9	11.8
Female	14	7.3	4.7	11.1
Holtzman				
Male	17	9.2	5.2	14.1
Castrate	13	11.0	4.7	10.5
Female	19	20.3	0.6	13.7
$MgNH_4PO_4 \cdot 6H_2O$ (Struvite)			9.9	12.6
$CaHPO_4 \cdot 2H_2O$ (Brushite)		23.2		18.0
$Ca_{10}(PO_4CO_3OH)_2$ (Carbonate-Apatite)		27.0		12.7

* For purposes of comparison, the per cent of Mg, Ca, and P in pure magnesium ammonium phosphate and in two insoluble calcium phosphates are given in the lower part of the table.

TABLE 2. *Chemical analysis of urine, average values*

STRAIN, SEX, AND SIZE OF GROUP*	URINE VOL.	CALCIUM	MAGNESIUM	PHOSPHORUS	AMMONIA N_2
	cc/day	*mg.%*	*mg.%*	*mg.%*	*mg.%*
Harlan					
12 Males	16.5	11.4	30.3	83.8	44.1
11 Females	10.	15.4	32.1	95.4	—
Holtzman					
11 Males	18.5	15.7	26.5	109.2	—
11 Females	11.	16.8	22.0	104.2	51.8

Statistical comparison Harlan males vs. Holtzman females:
Calcium mg.% $t = 3.81$, $p < 0.01$
Magnesium mg.% $t = 2.812$, $p < 0.02$

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* Urine collected and analysed from each rat for 3 days, except for ammonia nitrogen determinations, where 1 day collections were used.

no magnesium except for three instances where small amounts were found. The two remaining groups, Harlan females and Holtzman males, fell between the other two groups of rats, some producing almost pure "magnesium" stones, others almost pure "calcium" stones, while the remainder were of mixed chemical composition. As may be seen in table 1, castration of Holtzman male rats did not significantly alter the chemical composition of the stones when compared to uncastrated males of the same strain, though there is a slight tendency toward stones of higher calcium and lower magnesium content. At present we have not exactly identified the substance making up the "calcium" stones. Unfortunately stone analysis for carbonate was not made and the percentages of calcium and phosphorus in both pure brushite and pure carbonate apatite are about equally close to the percentages found in the stones.

Quantitative chemical analysis of the urine of the different groups, table 2, suggests some correlation of the crystalloid excretion and the type of stone produced. In the Harlan males, where "magnesium" stones were formed, the urinary magnesium is comparatively high while the calcium concentration is the lowest of the 4 groups. Conversely, in the Holtzman females, where calcium stones were formed, the highest average calcium concentration and the lowest average magnesium concentration were found in the urine. Ammonia excretion was found to be essentially the same in these two groups. The smaller average urine volume in the female animals is accounted for by the smaller size of the females. It may be added that in a later experiment further data were obtained (not shown in table 2), on the urinary crystalloid concentration of 12 male Harlan and 12 female Holtzman rats. This later experiment was similarly conducted and yielded the same relative differences as the experiment given in table 2; the magnesium excretion was distinctly high and the calcium excretion distinctly low in the Harlan male rats when compared to the Holtzman females.

DISCUSSION

It is evident from the results of this experiment that both the strain and the sex of rats influence the chemical nature of stones produced upon foreign bodies in the bladder. It should be emphasized that to all gross appearances the rats of the two strains were exactly alike. Yet it seems that inbreeding over many generations by the 2 commercial breeders has resulted in genetic changes which lead on the one hand to rats tending to produce stones predominantly composed of calcium salts and on the other of stones composed of magnesium ammonium phosphate. Within each strain there is also a sharp trend toward stones of higher calcium content in the female.

The only explanation so far available of the mechanism accounting for the differences in stone composition lies in the results on quantitative chemical analysis of the urine. Roughly speaking, both the rat strain and sex seem to influence the relative urinary concentrations of magnesium and calcium. Where "magnesium" stones were found, the urinary magnesium concentration tends to be higher and the calcium concentration lower. The converse is true, of course, for the groups tending to produce stones high in calcium content. The differences in urinary concentration are not striking, however, and to us do not appear entirely satisfying as an adequate explanation for the differences noted in the stones. On the other hand, it is hard to imagine that different chemical types of stone can result apart from differences in the urinary crystalloid concentrations. The experiments may, perhaps, illustrate that profound alterations in the process of stone formation may arise from apparently slight and subtle changes in the concentrations of the stone-forming crystalloids.

From an investigative standpoint the findings are of some practical importance in that by selecting the proper strain and sex of the rats used, it is possible to produce "calcium" stones for experimental studies similar to our previous investigations on "magnesium" urolithiasis. The results also point up the difficulty of carrying over the findings of experiments in rats from one experimenter to another on problems of stone formation if the particular breed and sex of the rats are not considered. In various papers in the literature on rat urolithiasis, workers have sometimes obtained stones of different chemical composition and have sought an explanation for these variations in diet, infection, or some other mechanism. The work presented here suggests that an additional explanation might possibly be found in differences in sex and rat strains used.

Clinically, these experiments may bear some relation to the variations in stone formation in the different human races, such as the lower incidence of stone in Negroes. At least the experiments illustrate that rather fine genetic differences may markedly influence stone formation. At present we are not aware of any information to show that either strain or sex in human beings alters the chemical type of stone produced in the urinary system.

SUMMARY

Experiments are presented to show that the chemical type (though not the incidence) of stone produced on foreign bodies in the bladders of rats is influenced by both the strain and sex of the rats used, even though the diet is the same throughout. It is possible by proper selection of strain and sex to produce stones of almost pure magnesium salts or pure calcium salts. Evidence is presented suggesting that relatively slight differences in the urinary concen-

trations of calcium and magnesium may account for the marked differences in the type of stone produced. Any rat experiment on urolithiasis must therefore take into account rigid control of not only the sex of the animals used but even the particular breeder from whom the rats are obtained.

ADDENDUM

Since this work was completed, a study was made of the stones produced in cross-bred rats of these two strains. Information is available on 19 male and 21 female cross-breeds of Harlan females X Holtzman males. The male cross-breeds tended to produce calculi more of the magnesium type than pure-bred Holtzman males, while the females produced calculi more of the calcium type than pure-bred Harlan females. When the pure strains were bred in the opposite way—Harlan males X Holtzman females—the eight male progeny produced pure "magnesium" calculi, while the eight female progeny produced pure "calcium" calculi. Thus, the tendency in these cross-breed experiments was to produce chemically homogeneous stones dependent more on the sex of the progeny than on the parent rats, confirming the marked influence of sex on stone type as reported in rats of pure strain.

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EXPERIMENTAL UROLITHIASIS VIII: FURADANTIN IN TREATMENT OF EXPERIMENTAL PROTEUS INFECTION WITH STONE FORMATION

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The experiments reported here have as their aim to determine the effectiveness of nitrofurantoin (Furadantin) against experimental Proteus infection of the urinary tract and in addition, to observe the value of this drug in combating the stone-forming propensities of the Proteus organism. It is well known that Proteus infection is, indeed, a potent factor in augmenting stone formation by virtue of its urea-splitting property. Infection of the urinary system with urea-splitting organisms is, of all of the conditions thought to favor stone formation, the most clearly established and undoubted. From the time of Brown[1] in 1901, urea-splitting infection has been considered by many authors to be one of the most important contributing factors in urolithiasis, particularly of the more severe varieties, and a frequent cause for recurrence of stones following surgical removal. Experimental confirmation of the relationship of urea-splitting infection and urinary stone is not lacking. Hagar and Magath,[2] Davalos,[3] Keyser,[4] and others have all demonstrated in animals a striking development of calculi when such infection is introduced, provided there is additional trauma to the urinary tract of one kind or another. It is, then, well established that given the presence of certain other conditions, urea-splitting infection will almost inevitably lead to the growth of stone by virtue of the ability of the enzyme urease to split urea and thereby increase the ammonia concentration and alkalinity of the urine, conditions which favor precipitation of relatively insoluble stone crystalloids.

Recently Furadantin, Eaton, a brand of nitrofurantoin[5, 6] has been recommended as a urinary antibacterial agent of value in infections with organisms heretofore not easily combated with existing agents. Among these infections is Proteus. Clinical experience with Furadantin has already indicated that it does have real value in the treatment of certain otherwise resistant cases of

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human urinary infections. It seemed to us that perhaps worthwhile observations could be obtained from a study of the effectiveness of Furadantin in inhibiting the marked stone formation that occurs in the presence of Proteus infection. The methods for the study of stone formation previously used by us seemed to lend themselves to such an experiment.[7,8]

METHODS

Adult white male rats of a single strain (obtained from the Harlan Small Animal Industry) were operated upon and a standard foreign body (3–4 mm. discs punched from a sheet of zinc) was inserted into each bladder. It has been previously shown that on a diet of Purina Fox Chow, the stone that forms about the foreign body is composed of $MgNH_4PO_4 \cdot 6H_2O$. At completion of the experiment it is possible to compare quantitatively the amount of stone produced in control and experimental groups by weighing the stones and subtracting the initial weight of the foreign bodies. In the present experiments, at the time of foreign body insertion, Proteus morganii infection was introduced by first immersing the foreign body in a 24 hour Brewer's broth culture of the organism. The Proteus organism used in this experiment was originally isolated from the peritoneal cavity of a rat in an unrelated experiment. In vitro tests indicated that it was a powerful urea-splitter. Identification of the organism as Proteus morganii was confirmed by the Bacteriology Department, University of Illinois.

A total of five groups of rats with bladder foreign bodies were used. Two groups, serving as controls, had the foreign body introduced without Proteus infection. One of these groups received Furadantin from the time of foreign body insertion. The other group, also uninfected, was left untreated. Proteus infection was introduced with the foreign body in the remaining three groups. One of the Proteus groups was left untreated. Another group was given Furadantin commencing 4 days after the operation and introduction of infection. The animals of the third infected group had been started on Furadantin two days prior to infection. The Furadantin was given to the rats by mixing the powdered drug (0.15 per cent) with their powdered food. With this diet it is calculated that 90 mg. of Furadantin per Kg. per 24 hours was administered to the rats. Both food and water were available to the animals at all times. In the groups receiving Furadantin, treatment was continued throughout the experimental period.

Ordinarily in our past studies on stone formation by the method of foreign body insertion, we have permitted the animals to grow stones in the bladder for a period of six weeks before terminating the experiment. In the present experiment, however, a period of three weeks was chosen because rats infected with Proteus have an exceptionally high mortality rate and few untreated Proteus-

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infected rats will live longer than three weeks Since even in this short time large stones are formed where Proteus is present, three weeks was considered to be sufficient to produce adequate stones Three weeks after the initial operation, the animals were anesthetized and the bladder again exposed Urine aspirated from the bladder was examined for its pH and cultures were made on blood agar plates and in Brewer's broth Many animals also had cultures made of each kidney, done by incubating a slice of the kidney parenchyma in Brewer's medium The bladder was now opened, and the stones removed and weighed Where secondary stones were found in addition to the principal foreign body stone, these "daughter" stones were not included in the stone weights given in this paper

RESULTS

When Proteus infection is introduced in the urinary system of the rat by the methods used in this experiment, relatively few animals will survive for more than three weeks if measures are not taken to combat the infection Within three to ten days of infection, the majority of the animals in the untreated group were dead with diffuse peritonitis or extensive upper urinary tract infection In the few untreated animals that survived the experimental period of three weeks, severe cystitis and pyelonephritis were found Table 1 indicates that of a total of 31 rats, only five succeeded in living to the end of the experiment A positive bladder urine culture for Proteus was obtained in all, and all had extensive Proteus renal infection bilaterally

As expected, the urinary pH was high in these untreated Proteus infected animals An average pH of 8 3 was obtained in the five surviving rats (pH in sterile controls averaged 6 86) As also expected, rapid stone formation occurred in the infected animals as indicated in table 2 In three weeks an average of 120 mg of stone was obtained as compared to an average of only 19 mg in the uninfected and untreated control group In addition, the Proteus infected rats exhibited striking formation of sand, gravel, and other "daughter" stones in addition to the principal stone formed on the foreign body In one animal, small stones were formed in the kidneys

The effect of Furadantin treatment on survival of Proteus infected rats is rather striking (table 1) Whereas only 16 per cent of the untreated animals survived for the period of three weeks, 67 per cent survived for this period if

TABLE 1 *Effect of Furadantin on survival and urine culture*

INFECTION INTRODUCED	FURADANTIN BEGUN	TOTAL RATS	TOTAL SURVIVING 3 WEEKS	SURVIVING RATS WITH PROTEUS RECOVERED IN URINE	PER CENT SURVIVAL
None	None	28	28	0	100%
None	At oper	14	13	0	93
Proteus	Pre op	29	26	3	90
Proteus	Post op	33	22	10	66 7
Proteus	None	31	5	5	16

TABLE 2. *Effect of Furadantin treatment on stone formation*

INFECTION INTRODUCED	FURADANTIN BEGUN	SURVIVING RATS WITH STERILE URINE		SURVIVING RATS WITH PROTEUS RECOVERED	
		Total Rats	Average Stone in mg.	Total Rats	Average Stone in mg.
None	None	24	19.4	0	—
None	At oper.	13	4.5	0	—
Proteus	Pre-op.	23	14.4	3	14.3
Proteus	Post-op.	11	10.3	10	36.8
Proteus	None	0	—	5	120.4

treatment was begun three days after the introduction of the infection. An even higher rate of survival was obtained if the rats were already under treatment at the time Proteus infection was introduced. Only three of the 26 surviving rats in the pre-treated group yielded a positive culture at the completion of the experiment, and it is possible that pretreatment with Furadantin prevented a "take" of the infection after inoculation. The ability of Furadantin to successfully combat Proteus infection that has already become established is, therefore, better seen in the group receiving delayed treatment. Here more than half of the animals were found to have eliminated the infection despite the presence of a foreign body or stone in the bladder. Of the 22 surviving animals of this group with delayed treatment, ten yielded a positive culture for Proteus from the bladder; in only one of these was a positive culture found in the kidney.

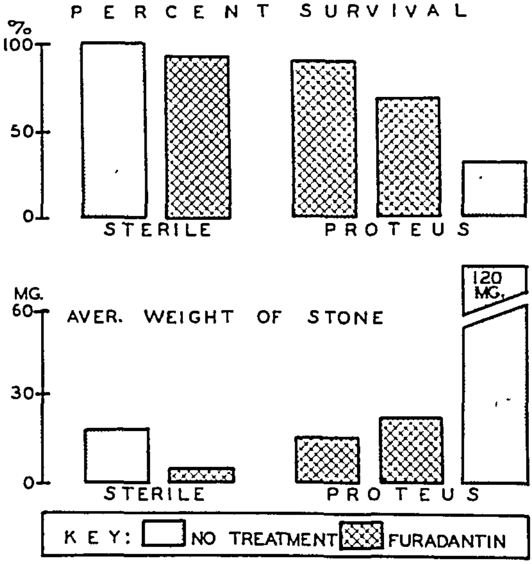

FIG. 1. Graphs showing per cent survival and average weight of stone produced on bladder foreign bodies in groups of rats indicated in tables 1 and 2. Two groups on left ("sterile") had foreign bodies implanted without infection. Three groups on right ("Proteus") had Proteus morganii introduced at time of foreign body implantations. Effect of Furadantin is seen in increasing survival and decreasing stone formation in rats infected with Proteus.

The urinary pH tended to be higher in the Furadantin treated animals if Proteus was still recoverable at the termination of the experiment The average pH was 7 79 for the 10 animals in the delayed treatment group where a positive Proteus culture was obtained at the end of the experiment This is distinctly higher than in the control group (pH 6 86) or in the animals which had eradicated the infection (pH 7 01) Likewise, as seen in table 2, the amount of stone formation that occurred was somewhat high, though not nearly so high as that seen in the Proteus infected untreated group Figure 1 graphically summarizes the pertinent data on survival and stone formation in the different groups of rats used in this experiment

DISCUSSION

As a method for testing the effect of drugs in urinary infection in animals, the foreign body technique used here would appear to be quite suitable because the foreign body prevents a spontaneous cure of the infection as so frequently occurs when even virulent organisms are simply introduced into the normal urinary system of animals In the present experiments it may be presumed that once the Proteus organism was introduced, spontaneous cure of the infection did not occur because all the untreated infected animals either died of Proteus infection or were found at sacrifice to have extensive urinary tract Proteus infection Therefore a final negative culture in any of our treated rats that had been initially inoculated with Proteus may be interpreted as the result of the treatment and not as a spontaneous occurrence

Since almost all of the rats yielded a sterile urine on final culture in the group that was already on Furadantin at the time the infection was introduced, it seems likely that in many of these cases the infection failed to "take" when the bladders were inoculated The results in the group where treatment was delayed are more interesting since we may assume that in all of them an actual Proteus infection had had opportunity to occur But even in this group, despite the presence of a foreign body, in about half of the rats a final culture failed to yield a positive urine culture It should be remembered, however, that the animals were still on Furadantin at the time this final culture was taken Recrudescence of the infection might have occurred if treatment had been stopped some days prior to final culture In the cases where infection was still present despite Furadantin treatment, it cannot be said that the medication was without effect, for at sacrifice severe bladder or kidney infection was not found, and marked stone formation was not observed

Since Furadantin is said to produce relatively low blood levels, one might be concerned with the possibility that while the urine became sterile due to the high concentration of the drug, the deep tissues, particularly the renal parenchyma, might continue to harbor the infection and that the infection would there run unchecked In the experiments here reported renal parenchymal infection was found in only one Furadantin-treated animal, and in this case a positive urine culture was obtained from the bladder However, it must be pointed out that the dosage used in our experiments was relatively very high, roughly about nine times the dosage recommended for human beings when calculated weight for weight. At the present time experiments are in progress to determine if smaller dosages would also effectively prevent deep parenchymal infection.

In any case, the experiments support the clinical evidence of the effectiveness of Furadantin in urinary tract Proteus infection. Apparently because of the difficulty in producing urinary infection for controlled experiments in animals, no observations have been reported heretofore on the effect of the drug in urinary infection experimentally produced. The remarkable effect found here suggests that the drug might conceivably sterilize the urinary tract in some cases of clinical urolithiasis with Proteus infection even in the presence of stone. The possibility also exists that small doses administered for extended periods of time, even though not sufficient to sterilize, might yet be sufficient to markedly impede the rapid stone formation that occurs in Proteus-infected patients. Whether such effects can be obtained with the drug will only be determined from clinical experience, but the experimental observations at least suggest these possibilities.

SUMMARY

Experiments are presented on the influence of Furadantin in rats with urinary Proteus infection in the presence of a foreign body in the bladder. The results indicate that Furadantin markedly increased the survival rate of infected rats. In half the cases it was capable of sterilizing the urine of rats infected four days before treatment was instituted. In those instances where sterilization of the urine was not obtained, the drug was effective in preventing the marked stone formation that occurs in uncontrolled Proteus infection. With the high dosage of Furadantin used in these experiments, renal parenchymal infection was prevented or inhibited in almost every instance.

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ADRENALECTOMY FOR PROSTATIC CARCINOMA

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Endocrine therapy for prostatic carcinoma is well established on experimental[1-4] and clinical grounds.[5-9] Gratifying responses to castration-estrogen therapy, however, are only temporary. No unequivocal cures have been reported.[10]

Huggins suggested in 1945 that lack of response, be it initial or following previous remission, was due principally to two factors, independence of the tumor to androgens and/or the continued presence of androgenic compounds elaborated by the adrenals.[11]

Following orchiectomy, in patients with prostatic carcinoma, there is a temporary fall in the 17-ketosteroid excretion in the urine, followed by a considerable increase, occasionally to 50 per cent above pre-castration levels.[12] It was postulated that this was due to enhanced adrenocortical activity, mediated through the pituitary gland. Estrogens may inhibit this rise.[13]

Clinically, in humans, one may observe adrenal hyperplasia or tumors with masculinizing or feminizing effects. These regress following operative removal of the hyperfunctioning tissue.[14, 15] In certain strains of mice gonadectomy has been followed by the development of adrenal tumors and evidence of increased androgenic activity.[16, 17] However, in the adult castrated rat large doses of anterior pituitary extract, rich in gonadotrophic and adrenocorticotrophic hormones produce no change in the prostate and seminal vesicles. Following castration of the human male, a compensatory increase in N hormone by the adrenal cortex, if it appears, does not prevent the development of deficiency symptoms.[15]

The prevailing opinion is that the normal adrenal cortex secretes androgens.[18]

Read at annual meeting, American Urological Association, St. Louis, Mo. May 12, 1953.
We wish to thank Drs. Ralph Jones, Jr. and Sylvan H. Eisman of the Robinson Foundation for help in caring for these patients. The Medical Division of the Merck Co., Rahway, N. J., generously supplied cortisone for these patients.

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In addition, conversion of cortical hormones to androgens may occur in the liver and in other tissues.[19, 20] The administration of large doses of cortisone to females with intact adrenals frequently results in acne and hirsutism.[18, 21] Following the administration of large doses of cortisone to people with intact adrenals or moderate doses to Addisonian patients,[21, 22] there is observed an increase in the urine of 17-ketosteroids and their intermediate precursor compounds (steroids with an alpha ketol side chain at carbon-17). In castrated adrenalectomized prostatic carcinoma patients, urinary active androgen excretion varies as the cortisone dosage. It also roughly parallels the level of 17-ketosteroids in the urine. Nevertheless, the urinary excretion of biologically active androgens, even after very large doses of cortisone (300 mg. per day), is less than that of normal men.[21, 23]

Total adrenalectomy has a nonspecific inhibitory effect on the rate of tumor growth of certain transplantable carcinomas and sarcomas in rats and mice.[24-28] Lymphoid tumors, on the other hand, respond with opposite effects. Following adrenalectomy the incidence of "takes" of transplantable lymphatic leukemia was increased and survival time decreased in successfully inoculated rats.[29] There is an increased incidence of spontaneous lymphatic leukemia in susceptible mice following adrenalectomy.[30] The 11-oxygenated cortiscosteroids can inhibit the growth of certain tumors temporarily. This has been observed in transplantable lymphosarcoma in mice,[31] the Walker carcinoma in rats[32] and in certain osteogenic sarcomas in mice.[31]

In humans the administration of cortisone or ACTH has produced a temporary regression of some lymphomatous tumors. All tumors recurred and had either a diminished or absent response to repeated therapy.[33] In man, cortisone has not caused demonstrable regression of tumors other than lymphomas, even though a feeling of well being, increased appetite, improved strength and a recession of fever are commonly noted.[34, 35, 36]

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TABLE 1. *Preoperative status of patients*

PATIENT	AGE	PREVIOUS THERAPY	EXTENT OF DISEASE	CLINICAL STATUS	ACID PHOS.	ALK. PHOS.
E. N.	53	Castration; estrogens (no response)	Local disease, extension lymphatic metastases	Urinary symptoms, lymphedema rt. thigh with pain	0.6	5.6
S. S.	55	Castration; estrogen; TUR (no response)	Local disease, skeletal metastases	Bone pain, urinary symptoms	0.4	19.6
C. W.	64	None	Local disease, compression fracture L. skeletal metastases	Bone pain	2.8	27.2
K. S.	65	Castration; estrogens; TUR (good response)	Local disease, skeletal metastases	Urinary symptoms, bone pain	1.4	25.9
E. F.	65	Castration; estrogens; TUR (good response)	Local disease, skeletal metastases	Urinary symptoms, bone pain	0.1	11.4
H. B.	49	Castration; estrogens (good response)	Local disease, skeletal metastases	Bone pain, urinary symptoms	0.7	3.9

A metabolite of adrenal cortical origin, 11-Hydroxyetiocholanone, appears in the urine of a significant number of patients with neoplastic disease, whereas it is rarely found in the urine of normal individuals. Abnormal amounts of normal steroids have also been demonstrated in the urine of patients with various cancers[37, 38] This indicates adrenocortical dysfunction, the exact significance of which is unknown at present.

RESULTS

Six patients with active disseminated prostatic carcinoma were adrenalectomized (table 1). Five had previous castration-estrogen therapy. One had no previous therapy. Objective criteria to measure the course of the disease process were body weight, hemoglobin, acid and alkaline phosphatases, and the size of either the primary or the metastatic lesions, or both. Changes in activity were considered as depending on both the course of the disease and upon subjective factors.

Five patients are living 356, 342, 200, 82 and 67 days respectively following operation (table 2). Two patients were unaffected by adrenalectomy, one died 90 days postoperatively and one is still living 67 days postoperatively.

Excellent subjective improvement was noted in 4 cases and objective improve-

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TABLE 2. *Effects of adrenalectomy*

PATIENT	POST OP. SURVIVAL DAYS	STATUS	CAUSE OF DEATH	RESPONSE	
				Subj.	Obj.
E. N.	60	Living		0	0
S. S.	90	Dead	Carcinoma	+	0
C. W.	85	Living		+	+
K. S.	198	Living		+	+
E. F.	333	Living		+	+
H. B.	355	Living		+	+

ment in 3 of those cases. Two patients had partial vesical neck obstruction which was relieved following adrenalectomy. Relief in one was temporary, lasting 9 months. The other has no obstruction 11 months to date. Three patients had definite regression of the primary tumor mass. In 2 patients the regression has lasted 11 and 3 months respectively.

Two patients had elevated preoperative acid phosphatase values which dropped to normal levels after adrenalectomy. The values are still within normal limits 90 and 330 days postoperatively. However, the latter patient had no additional signs of objective improvement. Weight gains were noted in 2 patients (4 and 5 kg. following adrenalectomy).

Four patients had significant subjective improvement with relief, especially, of bone pain. Two of these 4 had been bed-ridden with pain unrelieved by opiates. Both were ambulatory within 3 days following operation, although one had substantial but not complete pain relief. His pain has returned recently but is of much less intensity than formerly. Three patients were completely free of pain within 48 hours following adrenalectomy, including one with a compression fracture of the first lumbar vertebra. Pain relief is complete 330 and 90 days respectively in 2 patients. One other patient, who had 270 days of excellent subjective improvement, recently had partial return of his bone pain.

DISCUSSION

Some reactivated prostatic carcinoma in castrated estrogen treated patients responds favorably to adrenalectomy with subjective and/or objective improvement.

The nonspecific inhibitory effect of adrenalectomy on the rate of tumor growth observed in certain animal carcinoma and sarcoma may be present also in adrenalectomized humans with tumors. However, no regression of size in experimental animal tumors was ever reported. Retardation of growth rate would be extremely difficult to evaluate in humans. One could not distinguish between results of therapy and between tumor behavior as dependent upon the biologic potential of the tumor. Miscellaneous tumors in humans, excluding breast carcinoma, prostatic carcinoma, and lymphomas, were unaffected by adrenalectomy.[37, 38]

It is probable that the further elimination of androgenic substances is the main cause of favorable response following adrenalectomy in human prostatic cancer.

Huggins and Bergenstal,[39] West[40] and Harrison[13] have reported the effects of cortisone administration on prostatic carcinoma patients in relapse after previous castration estrogen therapy. Cortisone has produced subjective improvement It was of shorter duration and not so complete as that following adrenalectomy[37, 38, 13] No objective improvement had been observed[37, 38, 13] until recently However, in one patient unresponsive to castration and adrenalectomy, massive doses of cortisone produced evanescent subjective relief and a temporary drop in acid phosphatase [13]

Subjective improvement following adrenalectomy did not parallel objective improvement A dissociation between relief of bone pain and steady progression of skeletal metastases was observed This has been noted by other investigators [37, 38]

Huggins[37] has divided prostatic carcinoma patients into 3 groups depending upon their response to castration estrogen therapy In the first is found the majority of the patients who respond with regression of the primary tumor and the metastases In the second is found a smaller group, responding with regression of the primary tumor only And in the third is the smallest group with no response at all

Responses following adrenalectomy may be classified similarly but the relative size of the groups appears quite different from that following orchiectomy In none of our patients did we see regression of the metastases Of the 23 cases recently reported in the literature[12, 37, 38] only 2 had regression[13] of and one arrest[38] of the metastases

Our 2 cases without improvement had a poor response to orchiectomy Harrison[13] reported one similar case However, one can find in the literature 2 cases[13, 37] with a favorable response to adrenalectomy following poor response to castration estrogen therapy

These observations are consistent with our present knowledge of the behavior of prostatic carcinoma, especially in regard to response to endocrine therapy Clinically and experimentally prostatic cancer shows great variation in response to estrogen and after varying periods of growth becomes tolerant of estrogen Biologically the longer it grows, the more independent it becomes of hormonal environment [41] This may explain the much smaller number, proportionately, of adrenalectomized patients falling into groups 1 and 2, especially group 1 of Huggins' classification

The effects of castration on prostatic carcinoma are variable and supplemental estrogen may control some prostatic cancer not affected by castration alone Experimentally androgen is needed to initiate the growth of prostatic carcinoma though the amount needed may be small [41] Good response to adrenalectomy following poor response to orchiectomy is probably due to the reduction of androgens below a certain critical level particular to the cancer cells at that time It is well known, however, that the physiology of the individual cancer cell can change in successive generations both in transplants and in humans.[41] Thus the biologic potential of the individual cancer cell makes it impossible, at present, to predict the efficacy of hormonal therapy on an individual basis.

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SUMMARY AND CONCLUSIONS

Six patients with prostatic carcinoma underwent total adrenalectomy. Five had previous castration-estrogen therapy. Two patients showed no response. Four obtained subjective improvement and 3 objective improvement. Improvement is temporary.

Until more data are acquired and evaluated, total adrenalectomy for prostatic carcinoma remains an experimental procedure.

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UNDIAGNOSED, GROSS RENAL BLEEDING

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Most of the etiological factors giving rise to hematuria can be identified with present day diagnostic facilities. Fundamental to the utilization of mechanical aids to diagnosis must be the acumen of the searcher. Despite the most favorable co-ordination of physician and technical equipment, unsolved bleeding from the urinary tract all too frequently confronts every diagnostician and surgeon. Until better indices as to *benign* blood loss be evolved, useful renal parenchyma will perforce be sacrificed surgically in an honest attempt to ablate neoplasms early in their development.

No less than 15 separate conditions are listed by Lowsley and Kirwin as productive of hematuria.[1] Higgins diagrammatically indicates 36 lesions at various levels in the urinary tract that may account for the presence of erythrocytes in the urine.[2] This author emphasizes the imperious need for complete urological investigation in every instance of hematuria. In this review of 1600 cases of hematuria, he reports that an average delay of 2½ years elapsed between the first appearance of blood in the urine and the opportunity by a physician to establish the diagnosis. The most common forms of pathological process encountered as the basis for hematuria in his study are, in order, tumor, calculi, tuberculosis, infection and nephritis.

It is obvious that the incidence of a primary cause for urinary bleeding would vary with the type of case most frequently attended at any given, specialized clinic. However, the fear of overlooking an early malignancy stimulates urologists everywhere to conduct an exhaustive examination of every patient who presents this problem.

In recent years, Papanicolaou stains of the urinary sediment have proved of value in detection or corroboration of small (and thus, potentially curable by surgery) urinary tract neoplasms.[3, 4] Nonetheless, many tumors escape notice by this technique and are later recognized either radiographically or by biopsy of distant and often unusually located metastases.[5, 6, 7] Since no radioactive element specific for tagging abnormally located red blood cells within the body is known, this method of bleeding site differentiation cannot be exploited at the present time. In essence, the time-honored avenues of urological study, namely, physical examination, urinalysis, cystoscopy and pyelography comprise the tools

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for determining the cause of hematuria. More recently, aortography[8, 9, 10] and retroperitoneal pneumography[11] are finding places in the urologist's diagnostic armamentarium.

Mention in the literature of occasional and unusual cases of "obscure bleeding" from the kidneys or elsewhere in the urinary tract[12] fails to offer improved diagnostic measures.[13] Thus far, in this paper, all the procedures cited as diagnostic aids seek to obviate the use of open surgery. Weyrauch, Wanless, Goebel and Scott urge surgical exploration and biopsy of the kidney for suspected neoplasm before removal of this otherwise usefully functioning parenchyma.[14] Certain objections may be directed against their proposed method, such as the inherent danger of wound implantation of tumor cells at the time of positive surgical biopsy. Moreover, it is unfortunately almost a truism that kidney exploration commits the operator to extirpation when persistent doubt prevails in the operating room as to the nature of the lesion which produces hematuria.

The shortcomings of the entire gamut of diagnostic efforts in some instances of hematuria, even after the most thoroughgoing study, pose the problem for presentation of this communication. It is hoped that our addition of such cases to those already published may act as further stimulus for search of accurate, dependable, preoperative diagnostic methods. It is readily admitted that this report fails to suggest any such advance.

CASE REPORTS

The cases of renal bleeding selected for this study met in common the following basic criteria:

1) Blood was seen to spurt from a ureteral orifice during cystoscopic examination.

2) No renal disease could be discovered by intravenous and/or retrograde pyelography.

3) Absence of urinary infection was proved by bacteriological culture or by stained smear of the catheterized urinary sediment.

4) No hypertension or albuminuria was present.

Table 1 represents a summary of the salient features of 19 cases in which the cause of the renal bleeding was undiscovered. There were twice as many males (13 cases) as females (6 cases) in this series. Eleven Caucasians and 8 Negroes* were encountered. No age group appeared to be more frequently involved than another; the range was from 17 to 66 years. However, 14 of the 19 patients were under 45 years of age, representing a proportion of 73.7 per cent. Equal incidence

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* None of the Negro patients was found to have sickle cell anemia. No patient had any blood dyscrasia.

Table 1 *Summary of cases: Undiagnosed, gross renal bleeding*

CASE NO	AGE YRS	SEX	RACE*	BLEEDING KIDNEY	HISTORY OF HEMATURIA†	TREATMENT	LENGTH OF FOLLOW UP†	FINAL RESULT
1 J R	17	M	N	L	10 d	Nephrectomy	6 y	No further bleeding
2 W W	54	M	W	Both	31 y	L nephrect 12 yrs before	6 y	R kidney bleeding
3 J W de H	44	M	W	L	9 y	$AgNO_3$ lavage renal pelvis, p r n	5 y	Occas L kidney bleeding
4 G A S	55	M	W	R	6 m	Transfusions, finally nephrect	4½ y	No further bleeding
5 J M B	17	F	N	R	2 w	None	4½ y	Prompt cessation
6 W N J	36	M	W	L	19 y	None	1½ y	Hemat ceased
7 N W	35	F	N	R	2 d	None	1 y	Hemat ceased
8 B S	21	M	N	L	1 m	Transfusions, finally nephrect	1 y	No further bleeding
9 L B	47	F	N	L	2 m	None	3½ y	Hemat ceased
10 M C P	31	F	W	R	3 d	Vitamins C, K, transfusions	3 y	No further bleeding
11 S J D	38	M	W	R	2 d	? Total dental extraction	3 y	No further bleeding
12 C C S	66	M	W	L	5 d	None	3 y	Hemat ceased
13 P W	37	M	W	R	1 m	? Tonsillectomy	2 y	No further bleeding
14 O G P	34	M	W	L	3 d	None	2 y	Hemat ceased
15 A B P	19	F	N	R	2 w	None	18 m	Hemat ceased
16 J D	38	M	N	L	2 w	? Tumor→explor →nephrectomy	10 m	No further bleeding
17 J M	23	M	N	L	1 m	Profuse, irreg blood loss, → nephrectomy	10 m	No further bleeding
18 H F	43	F	W	R	9 m	None	6 m	Hemat ceased
19 D W	57	M	W	R	4 y	None	6 m	Hemat ceased

* N—Negro, W—White
† d—days, w—weeks, m—months, y—years

of bleeding from each kidney was found, and in 1 instance, bilateral bleeding occurred In the latter case, right renal bleeding began shortly after a left nephrectomy, and was observed cystoscopically when the patient first came to us for study, 12 years after surgery

Conservative treatment consisted of all the nonoperative methods commonly employed, including use of vitamins C and K, cobra venom, cortisone, blood transfusions and lavage of the affected renal pelvis with silver nitrate solution These appeared at best to be only palliative In most cases, unless profuse renal blood loss was manifest, a policy of watchful waiting was adopted Frequent pyelographic examinations were made, at about 3-month intervals or more often, when indicated That this policy was worthwhile in the preservation of renal tissue was indicated by the spontaneous cessation of the hematuria in 9 cases. In 2 cases, intermittent, moderate hematuria persisted.

A total of 5 nephrectomies was performed by us. In one situation (case 16) early tumor was strongly suspected preoperatively, and at surgery an indurated area was palpated in the lower pole of the kidney. Only dilated vessels within otherwise normal parenchyma were observed microscopically. In 2 instances, the renal bleeding was excessive and was uncompensated by blood transfusions (cases 4 and 8). In another patient the blood loss was massive and nephrectomy proved to be an emergent, life-saving procedure (case 1). Interestingly enough, in 1 case, blood transfusions and vitamin therapy sufficed to tide the patient over her phase of acute bleeding; the hematuria ceased spontaneously and permanently within 2 months (case 10).

Only conjecture can be made as to the possible existence of "focal infection" as a cause of renal bleeding. Two of our patients achieved complete and prolonged termination of renal bleeding after dental extraction and relief of pyorrhea (case 11), and tonsillectomy (case 13). At the time of the most recent examination, no recurrence of the bleeding could be found in either patient.

All follow-up studies, consisting minimally of physical examination, cystoscopy with retrograde pyelography and microscopic analysis of the catheterized urine from each kidney and the bladder, were performed within 3 months prior to the writing of this report.

Figure 1 illustrates typical pyelographic studies, revealing absence of any radiographically identifiable lesion that might explain the hematuria.

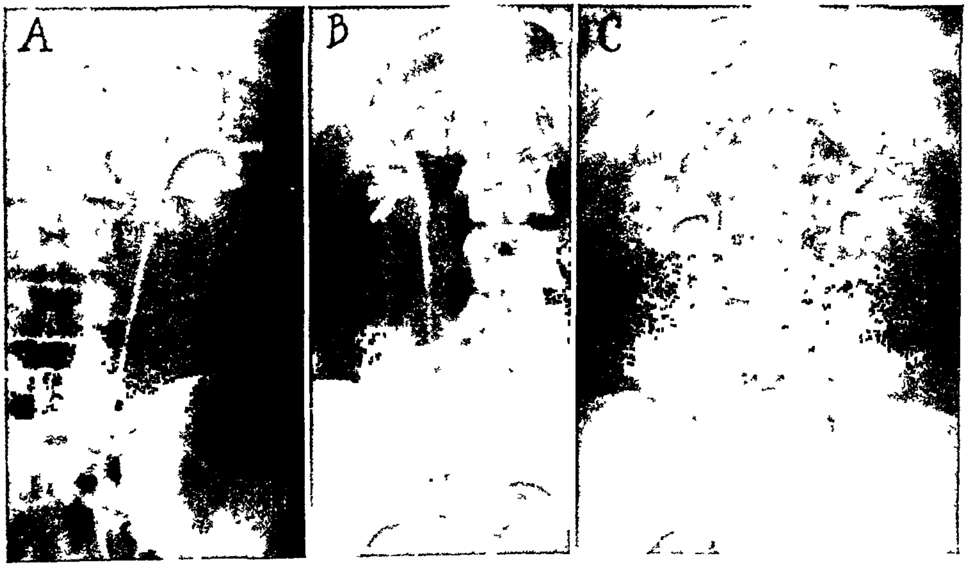

FIG. 1. *A*, case 3. Bleeding from left kidney began 1946. Constant bleeding except for short time after $AgNO_3$ lavages of renal pelvis. Unchanged pyelogram 3 years later is reproduced. *B*, case 10. Severe right bleeding began in 1950 and stopped 2 months after blood transfusions and massive vitamin C and K therapy in hospital. No recurrence by 1953, as depicted. *C*, *case 15* Painless bleeding of 2 weeks' duration in 1951, ceasing spontaneously after 2 months. Baby delivered normally in 1952. No recurrence of hematuria and patient again pregnant by February 1953.

DISCUSSION

The variety of titles assigned to undiagnosed renal bleeding attests, per se, to our ignorance of this process. Among these appellations are "essential hematuria,"[15] "idiopathic hematuria,"[16] "primary renal purpura,"[17-19] "chronic hemorrhagic papillitis,"[20-22] and, most recently, "palindromic renal purpura,"[13] to cite but a few. Fundamentally, the single purpose of all authors should be to classify these phenomena so that consistent diagnostic and therapeutic considerations may be applied in lieu of better knowledge at present of this type of renal bleeding.

In none of the specimens of the kidneys removed in the present series could eosinophiles be found in sufficient quantity to excite comment. Thus the report of Nation et al.[13] could not be corroborated here. The "chronic inflammatory and vascular changes in the papillae" described in some of Cahill's cases[23] were not characteristically nor commonly observed in our specimens. In brief, the histological pictures showed very little change, if any, as compared with normal, postmortem specimens of healthy adults.

Higgins contended that hematuria "if only on one occasion, means the presence of organic disease."[24] So broad a statement must be challenged in view of the spontaneous cessation of hematuria in almost 50 per cent of the patients reported in the present review. An organic cause would by definition necessarily suggest intrarenal changes beyond physiological alteration or ready reversibility. Conceding our clinical and laboratory limitations in detecting minute changes in a given patient's bodily economy, it is still perplexing that hematuria, often of many years' duration, should suddenly be relieved without features discernible to the physician. In any case, the self-limitation of this renal bleeding, in the absence of therapy, hardly signifies any known, severe organic disease.

In support of our argument, two revealing cases of prolonged, "nonorganic" hematuria may be excerpted from the many included in table 1. One patient (case 6) experienced persistent unilateral renal bleeding for 19 years; this ceased spontaneously and has not recurred during the past 4½ years. Another (case 3) has had benign, intermittent blood loss from one kidney for 9 years without ill-effect.

From a practical viewpoint, therapy must be arranged in accordance with the magnitude of the blood loss in the particular patient. If persistent, protracted bleeding does not adversely affect health, it may be assumed that compensatory mechanisms (increased erythropoiesis, etc.) are adequate to combat the disorder. Conservative management is urged. Temporization does no further harm, provided that the patient is carefully and judiciously followed. Avoidance of pre-emptory ablation of a bleeding kidney may well prevent the distressing situation wherein unexplained and possibly uncontrollable hemorrhage from a remaining kidney develops later. In two of our cases the patients refused surgery, which would most likely have been nephrectomy. Subsequently, these individuals enjoyed spontaneous remission without recurrence of renal bleeding for over 5 years.

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In addition to the 18 cases of undiagnosed renal bleeding, without pyelographic deformity, cited by McKay et al. in 1949,[16] about 11 other similar cases have been subsequently reported.[13, 14, 15, 19] Thus, the present study constitutes the largest single group of cases of undiagnosed, gross renal bleeding which has come to our attention.

SUMMARY

Nineteen cases of unexplained, gross renal bleeding have been presented. Most were males under 45 years of age. Complete urological studies were ineffective in identifying the cause or renal site of the hematuria. Nine patients enjoyed spontaneous and seemingly complete remission without treatment. Two others were relieved apparently following eradication of "focal infection". Five nephrectomies were performed because of profuse bleeding or suspected tumor. In none of the surgical specimens could histopathology be demonstrated to explain adequately the renal bleeding observed clinically.

No method of improved diagnostic facility was found. Conservatism, in order to avoid hasty nephrectomy, was recommended.

ADDENDUM

Since submitting our paper for publication, a report of 8 cases of unilateral renal bleeding of which 6 were controlled by vitamin K therapy has appeared (Strasberg, A. and Courteau, R.: "Essential Hematuria", Canad. Med. Assn. J., **68**: 253–255 1953). The vitamin was administered either during relatively brief hospitalization or by a "course of vitamin K". The Canadian authors suggested that " . . . prothrombin deficiencies will explain more and more of these cases of so-called 'essential hematuria' and that fewer nephrectomies will be the rule."

While we strongly support the goal of judicious conservation of normal kidneys, our experience does not coincide with that of Strasburg and Courteau either as to etiology or response to vitamin K therapy. Indeed, recurrence of bleeding, and even *de novo* hematuria from a remaining kidney, has been encountered during massive vitamin K therapy.

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ANEURYSM OF THE RENAL ARTERY

ROBERT L. ATKINSON

About one week before admission to the hospital on November 24, 1952, a 67 year old white woman experienced a slow onset of a dull ache in the low back region present daily with no preponderance as to side until the day of admission when it became more pronounced on the left with radiation around to the anterior abdomen and down the left thigh. There were no bladder signs or symptoms and no history of recent or old injury. In the past several years she had had intermittent, recurrent attacks of low backache which were not particularly disabling and not localized to one side exclusively. In 1947 the first attack of pain was associated with nausea and vomiting, but physical and laboratory examinations were nonrevealing. She was again seen by her physician in 1950 for a recurrence of the pain which responded to medication. The remainder of the past history is not contributory to this illness.

Physical examination revealed a somewhat obese white woman who was apparently not acutely or chronically ill. The blood pressure was 220/160. Neither kidney was palpable or tender and the abdomen revealed no masses, tenderness, or rigidity. All laboratory studies were within normal limits. Excretory urography and retrograde pyelography revealed normal structure and function of the kidneys and ureters. However, a radiopaque, annular shadow measuring 15 mm. diameter was located in the hilum of the left kidney slightly inferior and anterior to a very small renal pelvis. The shadow was incomplete in its superior portion and had a relatively radiolucent center. These radiographic findings were strongly suggestive of an aneurysm of the renal artery or one of its branches (fig. 1, *A* and *B*).

Under general anesthesia the kidney was exposed by the usual left lumbar approach. By careful dissection the renal vessels were isolated and stripped of adherent fat following which a chromic tie was placed around the pedicle. Distal to this a transfixation ligature was placed, the ureter was cut between chromic ties, and the kidney removed. A few seconds later considerable bleeding was seen coming from the region of the renal vessels which were then grasped with a curved Kelly hemostat which stopped the bleeding. A third chromic ligature was secured beyond the tip of the clamp. Because of the possibility of there being some inherent weakness of the vessel walls it was decided to leave the clamp in place and close the wound around it. This was done and the patient returned to her room in very good condition. There were no significant blood pressure changes noted during the operation.

The surgical specimen was examined several days after alternate freezing and thawing during the photographing of it, consequently the histological sections were too poor for accurate study. The kidney weighed 116 gm. and was quite soft and flabby. The capsule stripped easily leaving a smooth surface. The attached renal artery was deformed by a 15 mm. diameter spherical dilatation which was stony hard and located in the renal hilum (fig. 2, *A* and *B*). On section-

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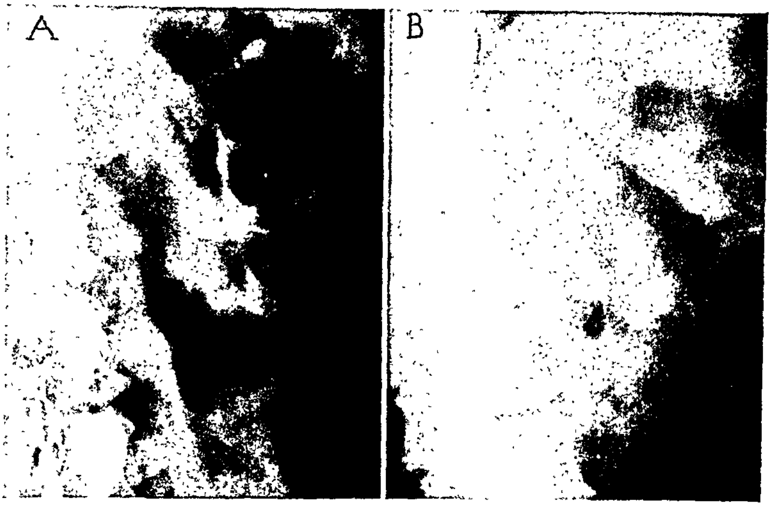

FIG. 1

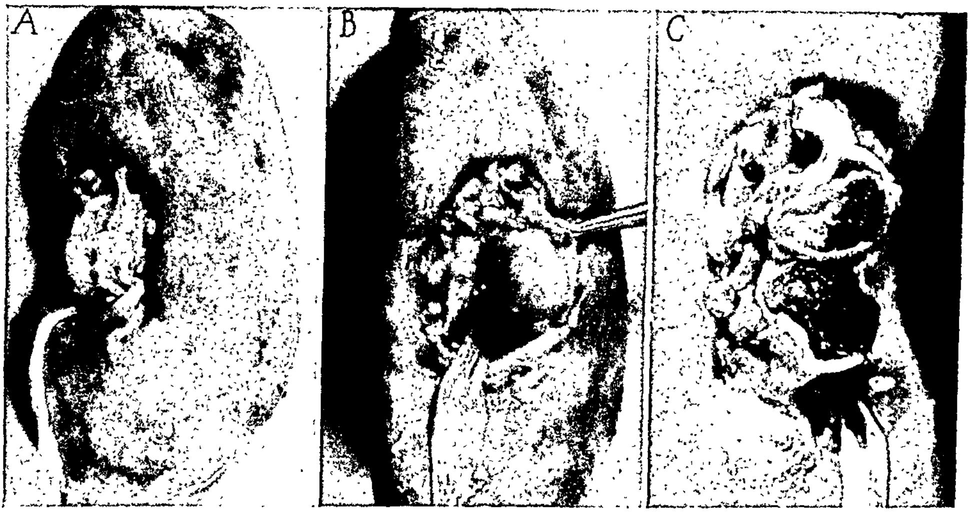

FIG. 2

ing the dilated area the knife was met with marked resistance due to the calcification of the walls which measured about 2 mm. in thickness. The lumen of the aneurysm was filled with brown-black, old hemorrhagic debris (fig. 2, *C*). Cut section of the kidney revealed fairly distinct markings.

On the fifth postoperative day the pedicle clamp was removed and the patient was discharged on the tenth day. About three months postoperative the blood pressure had remained at 180/110.

DISCUSSION

Aneurysms are classified as true and false. A true aneurysm is an outpouching of the vessel which is formed by one or more coats of the vessel. A false aneurysm is actually not an aneurysm but is a walled-off hematoma resulting from rupture of a normal vessel or of a true aneurysm. The incidence of true aneurysms is very low, there being only 80 cases reported. The latest survey of the literature was done by Abeshouse in 1951.[1] He reported a total of 115 aneurysms of which

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[1] Abeshouse, B. S.: Urol. & Cutan. Rev., **55**: 451–463, 1951.

35 were false Because false aneurysms are merely wall-off hematomas and resemble true aneurysms only because of their limitations by anatomical barriers, their inclusion in any statistical survey is not justified and serves only to confuse the real incidence of true aneurysms

The etiology is unsettled and debatable but the following points might be mentioned

1) *Inflammation* producing a weak area in the arterial wall is probably not important because only 1 of 80 cases reported had syphilis and there was only one case each of rheumatic endarteritis and tuberculosis

2) *Congenital causes* such as a developmental defect in the elastic tissue and media have been suggested but no definite proof has been offered

3) *Degeneration* such as arteriosclerosis plays an important part as seen in the finding of 12 such lesions in a series of 75 cases of both true and false aneurysms of the renal artery reported by Lowsley and Cannon

4) *Trauma*, in the past, has been over-emphasised as a cause of these aneurysms Mathé[2] reported a history of trauma in 23 of 55 cases, and Lowsley and Cannon[3] reported an incidence of 33 per cent of their 75 cases However, trauma probably is an important factor only after the artery has been weakened by disease

Hypertension has been reported in some of the cases as being related to the aneurysm and in others no definite relationship could be established Furthermore, several cases of associated hypertension were relieved by nephrectomy but many others were not significantly benefited

The prognosis varies with the treatment In Abeshouse's series of 115 cases of both true and false renal artery aneurysms 31 per cent were not operated upon and were dead within a variable period of time not greater than 5 years Various "conservative" operations such as partial excision of the aneurysm, exploratory operation, incision and drainage of a false aneurysm, denervation of the renal pedicle, kidney decapsulation and separation of the kidney from the aneurysm by division of adhesions resulted in a mortality rate of 53 per cent On the other hand, nephrectomy produced a mortality rate of 6 per cent in 53 cases

Treatment of renal artery aneurysms is generally regarded to be nephrectomy by most urologists When the diagnosis has been made or suspected nephrectomy is mandatory rather than merely advisable It is redundant to say that rupture of an aneurysm demands immediate operation Conservative operations are applicable in very few cases, Mathé has successfully excised an aneurysmal sac accidentally discovered during sympathectomy

SUMMARY

Aneurysms of the renal artery are quite rare and few reports are to be found in the literature The exact number of cases of true aneurysm is difficult to determine because of the inclusion of cases of so called false aneurysms The mortality rate is low following nephrectomy as compared with nonsurgical or conservative treatment

1510 N Clinton Blvd , Bloomington, Ill

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[2] Mathé, C P J Urol , 27: 667, 1932, 60 543, 1948

[3] Lowsley, O S and Cannon, E M J A M A , 121: 1137, 1943

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THROMBOSIS OF THE INFERIOR VENA CAVA AND RENAL VEINS WITH HEMORRHAGIC RENAL INFARCTION

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Hemorrhagic infarction of the kidneys due to thrombosis of the inferior vena cava and renal veins is an extremely rare entity as opposed to hemorrhagic renal infarction resulting from localized renal vein thrombosis. The literature is relatively abundant with reference to localized renal vein thrombosis[1, 2, 3, 4, 5] and to date, four such cases[4, 6] have been correctly diagnosed and nephrectomy performed, the most recent having been reported by Milburn.[7]

Weber and his co-workers[8] have reported 10 cases of thrombosis of the inferior vena cava occurring in adults varying in age from 28 to 62 years. Derow and his associates[9] reported one case occurring in a 15 year old boy and Lutembacher[10] reported a case of gradual obliteration of the inferior vena cava beginning at the age of 16 in which the patient survived 15 years. Most recently, Feriozi et al.[11] presented a case of thrombosis of the inferior vena cava and renal veins with hemorrhagic renal infarction occurring in a 4 month-old infant.

It is the purpose of this paper to present a case of extensive venous thrombosis including the femoral and iliac veins, the inferior vena cava and the renal and suprarenal veins associated with bilateral hemorrhagic renal infarction occurring in a 19 month-old female infant. Review of the literature fails to disclose a case of such extensive involvement occurring in infancy.

CASE REPORT

A 19 month old white girl was admitted to the Binghamton City Hospital on June 7, 1952 with the complaints of vomiting, diarrhea and gross hematuria. History revealed that on May 5, 1952, an afebrile illness developed characterized by severe vomiting and an excoriating diarrhea which gradually improved in about 3 days under conventional therapy with kaopectate and paregoric. In retrospect, the interval history was significant in the fact that the child appeared to experience lumbar pain on being picked up and also that she was reluctant to walk. On the day of admission, vomiting and diarrhea recurred and she passed a large amount of grossly bloody urine containing some clots.

Accepted for publication May 1, 1953.

[1] Abeshouse, B. S.: Urol. & Cutan. Rev., **49**: 661–665, 1945.

[2] Fallon, M. L.: Arch. Dis. Childhood, **24**: 125–128, 1949.

[3] Morison, J. E.: Arch. Dis. Childhood, **20**: 129–134, 1945.

[4] Sandblom, P.: Acta Paediat., **35**: 160–167, 1948.

[5] Kobernick, S. D., Moore, J. R., and Wiglesworth, F. W.: Am. J. Path., **27**: 435–449, 1951.

[6] Campbell, M. F. and Matthews, W. F.: J. Pediat., **20**: 604–615, 1942.

[7] Milburn, C. L.: J. Pediat., **41**: 133–140, 1952.

[8] Weber, F. P., Rast, H. and Wendt, L.: M. Press, **196**: 262, 1938.

[9] Derow, H. A., Schlesinger, M. J. and Savitz, H. A.: Arch. Int. Med., **63**: 626–647, 1939.

[10] Lutembacher, R.: Presse méd., **43**: 1175, 1935.

[11] Feriozi, D., Rice, E. C., Burdick, W. F. and Troendle, F. J.: J. Pediat., **38**: 235–241, 1952.

Physical examination on admission revealed an acutely ill, lethargic, moderately dehydrated infant with profound pallor of the skin and mucous membranes. The rectal temperature was 103.2F, the blood pressure 122/60 and the pulse 120 per minute. The remainder of the significant physical findings were limited to the abdomen where the superficial veins were markedly dilated and the abdomen was distended. There was tenderness to pressure and rebound tenderness throughout the entire abdomen and no peristalsis could be heard. A firm, tender, smooth, immovable, crescent-shaped mass was palpable in the left para-umbilical region. Catheterization obtained only a few cubic centimeters of bloody urine and rectal examination revealed light yellow feces on the examining finger.

The erythrocyte count was 2.25 million per cubic mm., hemoglobin 3.75 gm. with a color index of 0.51. The leukocyte count was 10,000 per cubic mm. with a differential count of 21 per cent lymphocytes, 1 per cent basophils, 2 per cent stabs and 76 per cent segmented polymorphonuclear leukocytes. The nonprotein nitrogen was 134.5 mg. per cent. An abdominal flat film showed no free air under the diaphragm and gas was seen in the large and small intestine but no unusual pattern or distribution was noted. A barium enema was considered as essentially normal and a chest film revealed only slight cardiac enlargement in the transverse diameter.

The infant was treated supportively and given daily whole blood transfusions of 150 cc. each on the first 3 days, fluids of glucose, saline and Ringer's solution, penicillin and vitamin K daily parenterally. A cut down was performed in the left ankle to facilitate intravenous therapy. During the first 24 hours following admission, the superficial abdominal vein dilatation and the abdominal distention subsided but both subsequently recurred. Two days after admission, bilateral ankle edema was noted, intravenous therapy was stopped for 24 hours and the cut down in the left ankle was discontinued. Three days after admission, cystoscopy and retrograde urography were done under ether anesthesia. At that time, although no urine was seen to enter the bladder, the lower urinary tract and retrograde urograms were considered normal. Abdominal examination under anesthesia revealed the previously described abdominal mass to be about four inches long and located just beneath the left costal margin in the midclavicular line. The red cell count had risen following the transfusions to 3.53 million with a hemoglobin of 9 gm. while the white cell count had risen to 17,900. On the third hospital day, the nonprotein nitrogen was reported as 91.5 mg. per cent and the blood chlorides as 425 mg. per cent. Following cystoscopy, intestinal intubation and hourly gastric lavage with tap water was instituted and 3 days after admission, the temperature had fallen to normal. The infant had only an occasional loose bowel movement and urination consisted of slight diaper saturation staining the diaper pink. The blood pressure ranged between 90 and 100 mm. of Hg systolic and 60 and 70 mm. of Hg diastolic. Five days after admission, the serum sodium was reported as 203.8 mg. per cent, the serum potassium as 18.95 mg. per cent, the blood chlorides as 380 mg. per cent and the nonprotein nitrogen as 104 mg. per cent.

The general condition of the patient had improved so that gastric lavage was discontinued on the sixth hospital day and she was able to retain fluids and soft foods. Despite the fact that she received only 300 to 900 cc of fluid a day, the urinary output improved somewhat but the diapers continued to be stained a light pink. Loose bowel movements had now ceased and the stools were soft but formed, varying in color from light yellow to dark brown and, except for one or two occasions, the vomiting had ceased. The first measureable amount of urine obtained eight days after admission revealed an insufficient quantity for specific gravity, a light greenish-amber color, an alkaline reaction, albumin 75 mg. per cent, 10 to 15 white blood cells per high power field, a few motile bacteria and amorphous phosphate crystals; no red blood cells or casts were seen. The nonprotein nitrogen at that time had risen to 145 mg. per cent and the blood chlorides were reported as 440 mg. per cent.

Two weeks after admission, lethargy and irritability recurred and became progressively worse along with superficial abdominal vein dilatation and abdominal distention despite the fact that the urinary output continued to improve. The nonprotein nitrogen continued to rise and 13 days after admission, it was reported as 193 mg. per cent. Liquid and soft nourishment were now refused and although penicillin therapy had been continued, the cut-down in the left ankle became infected. On June 25, 1952, fine, generalized tremors were noted and intestinal intubation with gastric lavage was re-instituted. The nonprotein nitrogen had risen to 313 mg. per cent and the following day, 20 days after admission, the infant expired following the onset of generalized convulsions.

Postmortem examination: The anatomical diagnoses were—massive acute infarction of the entire left kidney following thrombosis of the renal vein; multiple acute infarctions involving more than two-thirds of the right kidney following thrombosis of the renal vein and its branches; propagated thrombosis of the inferior vena cava superimposed on an organized phlebothrombosis of the femoral veins, the iliac veins and the inferior vena cava with recanalization; multiple recent and old anemic infarctions of both adrenal glands following thrombosis of the adrenal veins.

The postmortem findings of importance, both gross and microscopic, are as follows:

Kidneys: Both kidneys were hard and swollen but the surfaces were smooth. The left kidney was about twice the size of the right kidney and the capsules were thickened, stripping with difficulty. The left kidney weighed 170 gm. and was diffusely reddish-purple in color and on cut section, this color was seen to begin at the papillary portions of the medulla and extend peripherally toward the cortex where there was a narrow zone of pale yellow, swollen cortex remaining. The left renal vein was completely thrombosed with a brownish-purple clot. The right kidney weighed 70 gm. and on cut section, presented a number of discrete, well-demarcated, wedge-shaped areas of pale yellow necrosis in the cortex with some evidence of hemorrhage about these areas. The entire papillary portion of the medulla was a similar pale yellow color. Grossly, the main right renal vein was occluded with thrombotic material and many of the

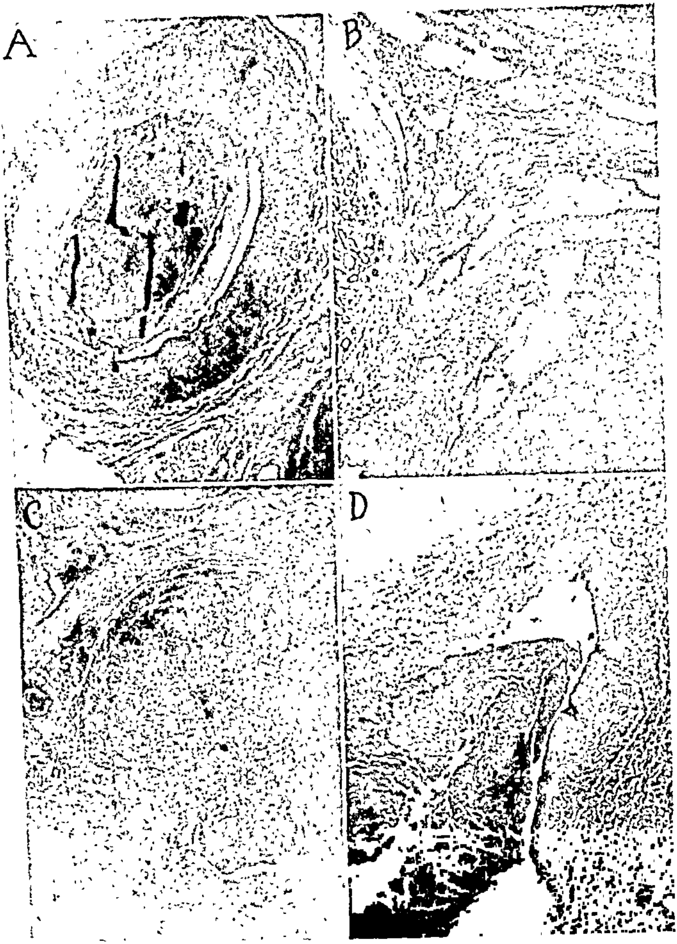

FIG. 1. *A*, low power view of main left renal vein showing complete occlusion by an organizing thrombus. *B*, low power section of right kidney showing partially thrombosed secondary renal vein. Note necrotic kidney tissue in upper right with normal kidney at bottom. *C*, low power view of left adrenal showing thrombotic venous occlusion with surrounding necrosis of medulla extending into portions of cortex. *D*, lower power view of inferior vena cava showing organized thrombus with evidence of recanalization.

secondary veins draining into the renal vein were thrombosed and occluded with old blood clots.

Microscopically, the left kidney revealed a complete, uniform antemortem anemic infarction of the entire kidney substance. Nearly all the renal veins (fig. 1, *A*) were greatly distended with blood clots and the collecting tubules were filled with large amounts of precipitated, granular acidophilic material in which round, deep pink staining albuminous bodies resembling red blood cells were seen. The cytoplasm of the kidney was granular and acidophilic and stained very poorly with complete loss of nuclei staining. The right kidney revealed well-formed glomeruli but the glomerular capillaries were congested and the Bowman's capsules were dilated. The convoluted tubules were greatly distended and the lining epithelial cells showed marked granular degeneration and exfoliation. Only a narrow margin of cytoplasm at the periphery of the epithelial cells was seen to be intact and some of the tubules were noted to be filled with albuminous material. The loops of Henle and the collecting tubules showed marked distention with granular, acidophilic material and the interstitial connective tissue, particularly that of the medullary portion, was edematous with irregular areas of interstitial, polymorphonuclear and mononuclear cell infiltration. Some of the renal veins were thrombosed and completely occluded with blood clots, the portions of renal tissue corresponding to these veins showing complete necrosis (fig. 1, *B*). The cells within this area of necrosis had completely lost their nuclei and were represented by granular, acidophilic material. It was felt that these anemic infarctions were of relatively recent origin.

Adrenals: Grossly, both adrenal glands were well-formed but atrophic and there was no evidence of hemorrhage. Microscopically, the adrenals (fig. 1, *C*) appeared to show two different types of lesions. In the older lesion, the cortex and medulla were completely atrophic and replaced by fibrous tissue while in the more recent lesion, there was evidence of acute adrenal hemorrhage which seemed to radiate from the medullary portion into the remaining viable cortical tissue.

Inferior vena cava: The femoral veins, the iliac veins and the distal two-thirds of the inferior vena cava were thrombosed with evidence of recanalization. Microscopically, approximately three-fourths of the circumference of the inferior vena cava was thrombosed and recanalized (fig. 1, *D*). There was evidence of chronic inflammatory reaction in the surrounding adventitia.

DISCUSSION

Hemorrhagic infarction of the kidney is a very rare disease, usually encountered in the neonatal period, of the most serious magnitude with an extremely poor prognosis for recovery. Kobernick and his associates[5] state that in terms of total necropsies, the incidence of this disease is less than one per cent. A review of the literature[7] indicates that only 258 cases of this disease have been reported and in only four of these has the diagnosis been made clinically and nephrectomy performed with survival of the patient. Approximately one-half of these cases have been unilateral in involvement and there seems to be no predilection for either side or for sex. Bilateral renal involvement is much more serious than unilateral involvement but Fallon[2] has reported a case of bilateral renal vein thrombosis with renal infarction in a newborn infant where the diagnosis was made clinically and in which recovery was spontaneous When the involvement is unilateral, Campbell and Matthews[6] state that about seventy-five per cent of the patients should be expected to survive when nephrectomy is promptly performed and when sepsis is not marked It is therefore apparent that the diagnosis should be made as early as possible in the course of the disease so that the patient may be afforded the benefits of surgery

A definite cause for renal vein thrombosis has yet to be advanced and thus it is in the case which we have just presented However, a number of predisposing factors have been postulated and Milburn[7] classified these generally as inherent and acquired Nevertheless, the main etiologic factors have been listed as dehydration, infection, bed rest and possible anatomic factors [5, 10, 12] In the cases of renal vein thrombosis which have been reported previously, it was felt that the thrombosis originated in one kidney and then extended to the other kidney via the vena cava In the case which we have presented, an organized and partially recanalized thrombus was found in the femoral veins, the iliac veins and the inferior vena cava Because of the recanalization evident in the distal portion of the vena cava, the thrombosis can only be explained on an ascending basis Since the infant had an entirely negative past medical history, it is believed that the original episode of thrombosis occurred when she first became ill approximately one month prior to hospitalization This would have been an adequate period for organization and recanalization of the thrombus and the involvement of the renal veins was felt to be secondary to the thrombosis in the inferior vena cava and not, as is usually seen, a localized process commencing in the kidneys

Early diagnosis is complicated by the fact that renal vein thrombosis with hemorrhagic renal infarction is a very rare condition and therefore, the diagnosis may not be entertained by the clinician until the process has so extended that nephrectomy would be valueless Unless the condition is recognized and nephrectomy performed within a period of time measured in hours or a few days, death will ensue Death results from uremia, the opposite kidney becoming involved in the thrombotic process by extension of the thrombus to the opposite renal vein via the inferior vena cava or from renal failure resulting from renal insufficiency of the opposite side and/or thrombosis and infarction of the kidney of the involved side

However, it should be emphasized that renal infarction due to renal vein and inferior vena caval thrombosis is not necessarily limited to the neonatal period as evidenced by the case which has just been presented in which this disease occurred in a 19 month-old female Previous reference has been made to cases presented by Weber and his co-workers,[8] Derow[9] and to Lutembacher[10] in which renal infarction associated with thrombosis of the renal vein and inferior vena cava occurred in adolescents and adults Likewise, thrombosis of the renal vein per se is also not limited to the neo natal period Danhiez[13] and Melick and

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[12] Zuelzer, W W Kurnetz R and Fallon R Am J Dis Child, 81: 27–38 1951

[13] Danhiez, P J d'urol, 23 481–495 1927

(fig. 1, *A*) were greatly distended with blood clots and the collecting tubules were filled with large amounts of precipitated, granular acidophilic material in which round, deep pink staining albuminous bodies resembling red blood cells were seen. The cytoplasm of the kidney was granular and acidophilic and stained very poorly with complete loss of nuclei staining. The right kidney revealed well-formed glomeruli but the glomerular capillaries were congested and the Bowman's capsules were dilated. The convoluted tubules were greatly distended and the lining epithelial cells showed marked granular degeneration and exfoliation. Only a narrow margin of cytoplasm at the periphery of the epithelial cells was seen to be intact and some of the tubules were noted to be filled with albuminous material. The loops of Henle and the collecting tubules showed marked distention with granular, acidophilic material and the interstitial connective tissue, particularly that of the medullary portion, was edematous with irregular areas of interstitial, polymorphonuclear and mononuclear cell infiltration. Some of the renal veins were thrombosed and completely occluded with blood clots, the portions of renal tissue corresponding to these veins showing complete necrosis (fig. 1, *B*). The cells within this area of necrosis had completely lost their nuclei and were represented by granular, acidophilic material. It was felt that these anemic infarctions were of relatively recent origin.

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PAINFUL NEPHRECTOMY SCAR

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Painful postoperative scars have been reported as resulting from cutting, traumatizing, or interrupting nerves; or from ligation of nerves along with vessels. A painful fibroneuroma subsequently develops.[1, 2] Moreover postoperative pain has been attributed to adhesions, muscle spasm, and neurosis.[2] It is believed that a further cause of postoperative pain is hereby worthy of presentation.

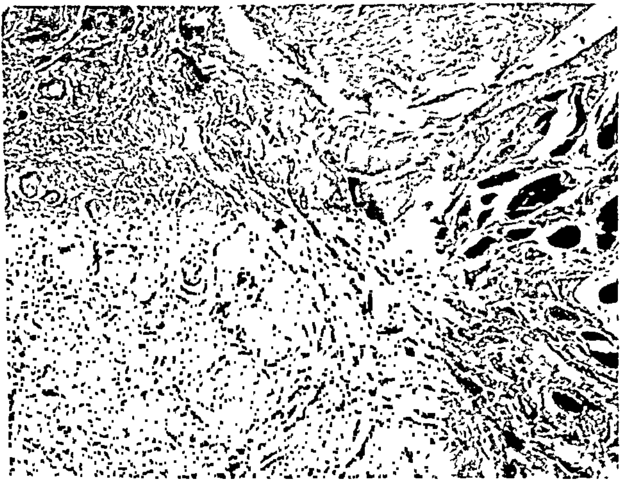

FIG. 1 Hyalinized glomeruli and scar tissue, left; fascia above; and skeletal muscle, right.

CASE REPORT

A 38 year old woman stated that she had always had left back pain even as a child. During her second pregnancy, 9 years before admission, the pain became worse and this was more pronounced after delivery. Subsequent investigation revealed a grade 2 hydronephrosis with marked obstruction at the ureteropelvic junction.

A left nephrectomy was performed on July 1, 1950. The operative note stated: "...A left lumber incision.... While cutting down into Petit's triangle, a cavitation entered which bled profusely. Upon further examination, after ob-

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Accepted for publication March 6, 1953.

[1] Bancroft, F. W.: Painful postoperative scars. Arch. Surg., **21:** 293, 1930.

[2] Corbett, J. F.: Painful scars. Minn. Med., **4:** 683, 1921.

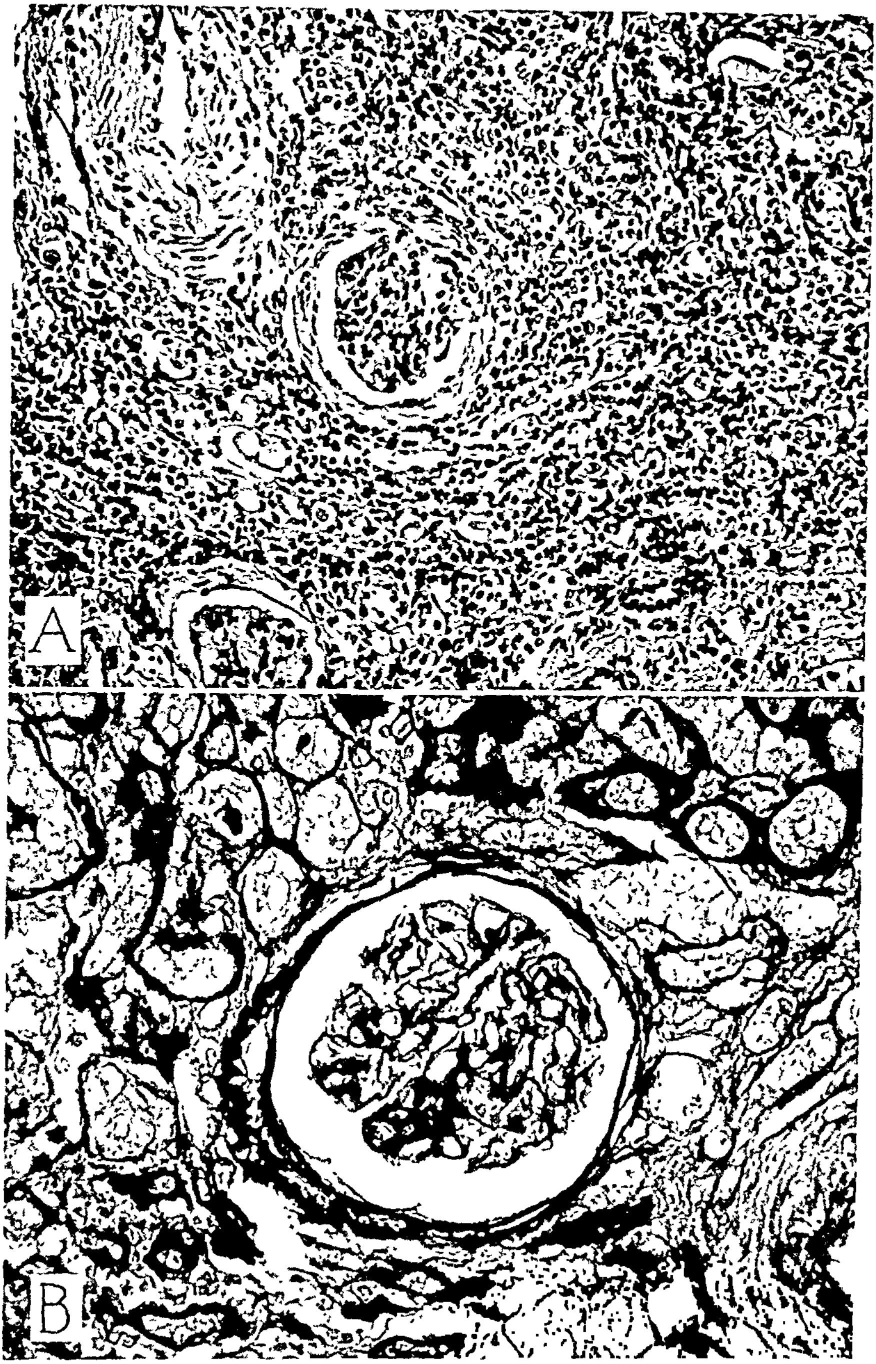

Fig. 2. *A*, kidney tissue showing chronic pyelonephritis and arteriosclerosis. *B*, functioning glomerulus and tubules.

taining access to retroperitoneal space, it was seen that the kidney parenchyma itself was opened into. The kidney was then freed with great difficulty. There was marked scarring and fibrosis completely surrounding kidney. . . ." The pathological diagnosis was chronic pyelonephritis.

Six weeks after the operation she began to complain of needle-like pain in the scar radiating to the left hip, groin and medial aspect of the left thigh. Later the pain changed to a persistent dull one with occasional sharp jabs. The pain was of sufficient severity that she required multiple nerve blocks every 3 weeks and the use of narcotics with but transient alleviation of symptoms. Examination disclosed a left flank scar with tenderness at the junction of middle and dorsal thirds The remainder of the history and physical examination was not remarkable

A second operation was performed 2 years after the nephrectomy (July 31, 1952). The old scar was excised under general anesthesia. Dense fibrous tissue was traced down to the fascia where the fibers seemed to penetrate what appeared to be the old drainage site through the muscle. No nerve was seen.

She was discharged on August 10, 1952 (tenth postoperative day), and was seen in the office on August 29 and November 1 The wound seemed well healed and there was no pain or tenderness.

The pathological specimen exhibited skin, 23 by 1 cm , with subcutaneous tissue, fascia and skeletal muscle 1 cm. deep. In the skin there was a linear scar, while 2 cm below the surface there was an indefinite area of induration 1.5 cm. in diameter. Microscopic examination of the latter demonstrated, amidst fascia and skeletal muscle (fig. 1), functioning kidney tissue with evidence of chronic inflammation (fig. 2). Nerve bundles were seen but no fibroneuroma was encountered

SUMMARY

A case is presented in which a painful postoperative nephrectomy scar is thought to have resulted from a small focus of residual functioning chronically inflammed kidney tissue situated in the deep fascia.

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GIANT HYDRONEPHROSIS; ONE STAGE NEPHRECTOMY

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The problems involved in the management of giant hydronephrosis are well documented in the literature. An excellent and comprehensive review of this subject was presented by Earlam who reported one containing 18 liters of fluid which was nephrectomized in two stages. The differential diagnosis from ascites and ovarian cysts is important, since these abdominal enlargements are produced by fluid. The history obtained from individuals with ascites will usually reveal a prolonged recurrent or progressive disability related to cardiac or hepatic disorders. A woman with an enlarged ovarian cyst or a patient with a giant hydronephrosis may never have been incapacitated, but only concerned with the nuisance of a steadily enlarging abdomen. Shifting dullness and flank distention on recumbency tend to aid in the clinical differentiation of these disorders since encapsulated cysts or a distended renal pelvis usually do not reveal shifting dullness and flank distention on recumbency. The danger in confusing these entities will often lead to trocar drainage, and there is the specific danger of infection from this procedure in giant hydronephrosis.

CASE REPORT

A 72 year old white man was admitted to the hospital in June 1951 with a chief complaint of a "swollen belly." The patient stated that he had noticed progressive enlargement of the abdomen for the past 10 years. He gave no history of pain, except for one episode 2 weeks prior to admission, when he experienced severe abdominal pain which was localized in the left flank and associated with grossly bloody urine. This patient had been unable to work for several years due to the enormous enlargement of the abdomen, although he had not experienced any weakness.

He had always been well and had engaged in farming most of his life. He gave no history of shortness of breath, swelling of the ankles, precordial pain, or jaundice. Three months before hospitalization he was treated at home for pneumonia, from which he recovered promptly. He gave no history of any surgical therapy.

The patient was well nourished. Only the abdominal findings were of significance. There was gross enlargement of the abdomen which measured 45 inches in girth (fig. 1, *A*). It was tense and the costal margin of the ribs flared outward. The abdomen was entirely dull throughout and no peristalsis could be heard. There was no shifting dullness.

The x-rays revealed marked elevation of the left leaf of the diaphragm. Two large calculi were visualized, one of which was a large staghorn stone below the lower pole of the right kidney, and the second was an unusually large round calculus in the lower left ureter (fig. 2, *A*). The excretory urograms showed a normal right renal pelvis with the ureter displaced to the right (fig. 2, *B*). No

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The material in the paper formed the basis of a scientific exhibit at the annual meeting, American Urological Association, Atlantic City, N. J. June 23–26, 1952.

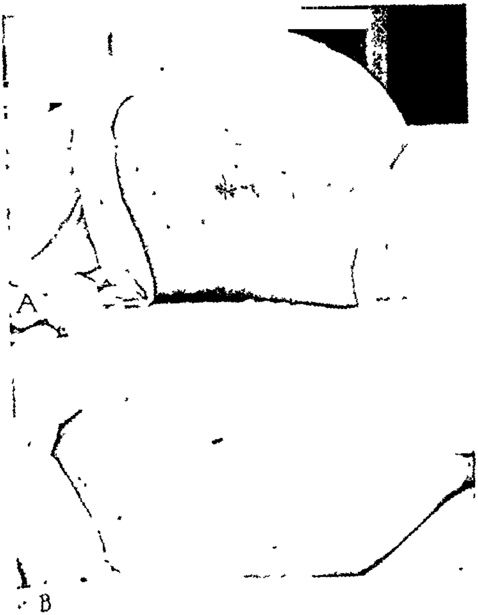

FIG. 1. A, patient on operating table. Waist measurement 15 inches. B, postoperative waist measurement 36 inches

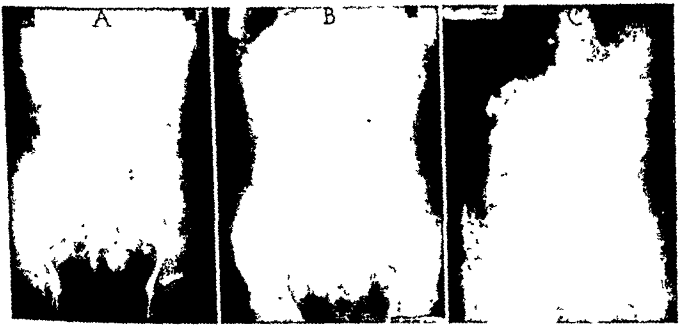

FIG 2 A, plain x-ray reveals staghorn calculus below right kidney, and large, round stone in lower left ureteral region B, excretory urogram shows normal right renal pelvis with ureter displaced to right No dye visualized in left renal area C, upper gastro intestinal series shows small intestines displaced to right side of abdomen

excretory dye was visualized in the left renal pelvis The stomach and small intestines were displaced to the right (fig 2, C). The transverse colon was displaced upward, while the descending and sigmoid colon appeared to be displaced to the left.

During the cystoscopic examination the left ureter could not be catheterized beyond the intramural portion.

The operation consisted of a one stage nephrectomy using endotracheal anesthesia. A cutaneous ureterostomy was done through a left flank incision. Ten liters of old blood tinged urine were aspirated from the left renal pelvis. There was loss of some fluid when the pelvis was opened. From a separate loculated mass within the renal pelvis an additional two liters of clear amber urine was obtained. The cultures of both specimens were sterile. The staghorn stone was impacted at the left ureteropelvic junction.

The patient's convalescence was prompt and uneventful. He was discharged from the hospital on his twelfth postoperative day (fig. 1, *B*). The postoperative abdominal girth measurement was 36 inches in comparison to 45 inches preoperatively. Slight drainage occurred from the cutaneous ureterostomy for 3 months, followed by firm healing.

SUMMARY

A giant hydronephrosis of 12 liters is reported in a 72 year old white man. The diagnosis was made preoperatively. Following the one stage nephrectomy the patient had an uneventful recovery. Differential diagnosis is important as trocar drainage is occasionally performed on these patients resulting in serious complications.

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THORACIC KIDNEY

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A case of congenital thoracic ectopy of the left kidney is described because it represents a rare condition which, while largely asymptomatic, may pose an interesting diagnostic problem.

We have been able to find 10 cases described of congenital thoracic kidney in the available literature. We are reporting this patient making a total of eleven. We also reviewed 2 cases of traumatic herniation of the kidney through the diaphragm, which were symptomatic, and were diagnosed while searching for the cause of chest pain and cough, and costovertebral angle pain. Of the ten reported cases, four were associated with other viscera misplaced into the chest, and only two of these were symptomatic.

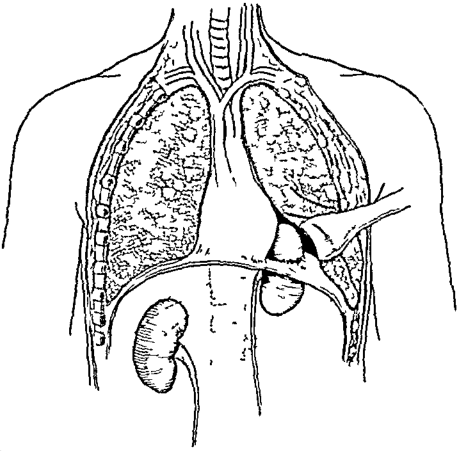

Fig 1. Left kidney protruding through persistent diaphragmatic foramen

Renal ectopy is not uncommon. In Campbell's autopsy series, it occurred once in 800 cases, most of which were displaced into or toward the pelvis. Crossed ectopy and medial displacement are occasionally seen, but diaphragmatic herniation with thoracic displacement is decidedly rare. The mechanism of the latter is probably failure of caudal migration of the mesonephros with associated persistence of the diaphragmatic foramen (fig 1).

A 64 year old Negro was admitted to the urology service with a clinical diagnosis of benign prostatic hypertrophy and early carcinoma of the prostate. He denied present or past symptoms of lung, diaphragmatic, or gastro intestinal

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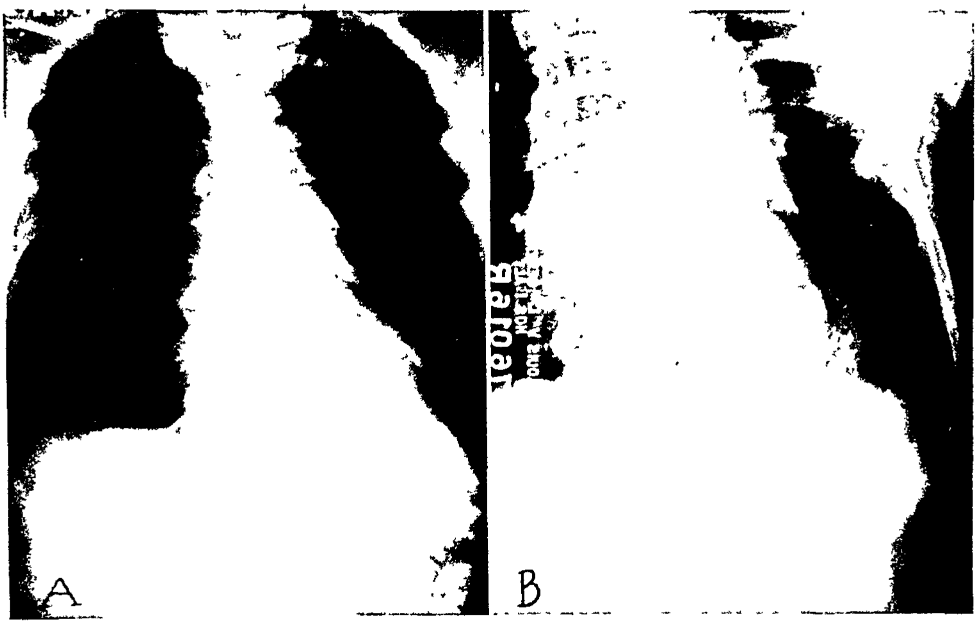

Fig. 2. *A*, admission film showing dome-shaped mass protruding through diaphragm. *B*, retrograde pyelogram, oblique view.

disease. He gave no history of previous accident or operation. The positive physical findings were limited to the prostate gland. The admission chest film showed a dome-shaped mass protruding up from the left diaphragm partially masked by the cardiac shadow, and was thought to represent a tumor of the diaphragm (fig. 2, *A*). Gastro-intestinal examination showed the small and large bowel to occupy normal position. Excretory urography and retrograde pyelography demonstrated the mass to be a morphologically and functionally normal kidney. The upper pole was at the level of the eleventh thoracic vertebra, about 5 cm. above the diaphragm (fig. 2, *B*).

A total retropubic prostatectomy and seminal vesiculectomy was done without incident, the pathologic diagnosis being adenocarcinoma in nodular hyperplasia. No exploration of the kidney was done. The patient has remained asymptomatic for three years without evidence of recurrence or spread of carcinoma.

SUMMARY

A case of asymptomatic congenital herniation of the kidney into the chest is reported. There are ten other recorded instances of this defect, and an additional two cases which were thought to be due to previous trauma.

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PAPILLARY ADENOCARCINOMA OF THE KIDNEY, WITH AORTOGRAPHY RESEMBLING HUGE RENAL CYST

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Aortography has become a widely accepted procedure from the number of arteriograms reported. The chief source of worry in this procedure has been a safe contrast substance which today has been alleviated considerably. The ideal medium should have a low viscosity, low toxicity, extreme x-ray density and be practically nonirritating.[1]

A great disadvantage of arteriography at present has been the limitation of the number of x-ray exposures which is limited to one picture during the injection showing the renal blood flow, and the second just after the injection which outlines the kidney substance (nephrogram). Serial x-rays, with prolonged injection of the ideal medium, will advance the use of this procedure considerably.

VALUES OF ARTERIOGRAPHY

The potential kidney function is in direct relationship to the blood supply of that organ and arteriography offers a visual evaluation of that blood supply. The vascular pattern in normal kidneys is typical, therefore, abnormalities in the arterial pattern are important. It is helpful to the urologist in differentiating avascularity in a space-consuming lesion presumably due to a cyst, in contrast to the pooling and puddling of the contrast medium which is supposed to be pathognomonic of tumor.[2] However, we wish to point out that arteriography, despite its usefulness, may occasionally be misleading, as in the case to be presented.

CASE REPORT

A 61 year old white waiter was admitted to McCook Memorial Hospital in September 1952 complaining of pain in the right side of the abdomen of about 1 year's duration He had also been aware of a fullness and mass in the right side of the abdomen for about one year.

During the 2½ years prior to this admission, he had had 3 admissions to another hospital, each time for severe glossopharyngeal and trigeminal neuralgia, and he had had 3 neurosurgical procedures for the relief of pain During these admissions, the following significant facts were brought to light: On the first admission, in May 1950, pulmonary tuberculosis was suspected on x-ray, but could not be proven on clinical or laboratory findings, including gastric washings On the second admission to the other hospital, in March 1951, a large, firm nontender mass was found in the right upper abdomen Plain x-rays of the

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Read at a meeting of the New England Section, American Urological Association, Hartford, Conn , April 30, 1953

[1] Melick, J W , Byrne, J E and Boler, T D The experimental and clinical investigation of various media used in translumbar aortography, J Urol , 67: 1019, 1952

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abdomen and barium enema were diagnosed as showing hepatic enlargement and the patient was told he had a fatty liver. The chest x-ray was unchanged. The third admission, for section of the fifth cranial nerve, added no further data.

During the 17 months between the last admission to the other hospital and the present admission to McCook, the following facts were brought to light:

1) He had lost 36 pounds in the past year despite an apparent increase in the size of his abdomen.

2) He had had 3 episodes of hematuria, the last one being 6 months previously.

3) He believed that the abdominal mass itself had increased in size.

4) He had some dyspnea on exertion but no chest pain or ankle edema. Hemoptysis was denied.

In summary then, we have a 61 year old white man who had several operations for trigeminal and glossopharyngeal neuralgia, the last one 17 months previously and apparently very successful. The mass in the abdomen discovered on these hospitalizations was thought to be an enlarged fatty liver, although all liver function studies were normal. During each of these admissions to the other hospital, the urine showed 1 plus albumin, 1 plus white blood cells and 1 plus red blood cells, but no other genito-urinary studies were done except a nonprotein nitrogen determination which was always normal.

The patient was referred now to the McCook Memorial Hospital by a physician who was seeing him for the first time, his impression being "carcinoma of the colon with metastases to the liver." When seen in the admitting room at McCook, he was referred to the urology service because of the episodes of gross hematuria and the ballotable mass in the flank. The attending surgeon and resident who saw the patient felt that the mass was most likely kidney.

Physical examination showed a well developed man of 61 who did not appear to be acutely ill. Vital signs were normal and the head and neck, heart and lungs were normal. There was no adenopathy and no loin tenderness. There was a huge mass in the right side of the abdomen extending from the costal margin to the anterior superior iliac spine and across the midline to about 2 inches to the left of the midline. The mass was ballotable in the flank, was about the size of a large honeydew melon, very smooth and resilient.

The genitalia were normal. Rectal examination showed a 2 plus benign prostatic enlargement. The extremities and nervous system were intact grossly.

The impression on the admission examination was cyst or hydronephrosis of the right kidney—this was chiefly because the mass felt like a cavity containing fluid.

Laboratory data showed 1 plus albumin, 2 plus white blood cells, and microscopic hematuria. The hematocrit was 37 and the remainder of the hemogram was normal. Sedimentation rate was 38 mm/hr. The nonprotein nitrogen was 36 mg. per cent. Total proteins were normal. Feces were negative for occult blood. Bleeding and clotting time were normal and prothrombin time was 50 per cent.

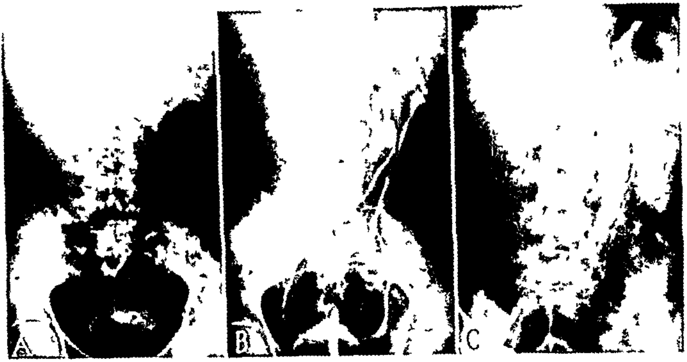

FIG 1 A, excretory urogram showing mass in right side of abdomen with nonfunctioning right kidney B retrograde pyelogram showing distortion of right renal pelvis and calyces with medial displacement of right ureter C aortogram obtained by translumbar aortography showing displacement of aorta and paucity of vessels in right renal mass

The x-rays were very interesting The chest x-ray on admission showed an arteriosclerotic aorta and bilateral apical tuberculosis, fibrosed, and considered inactive or healed

The excretory urogram showed a normal left kidney, but no function was discernible on the right The right side of the abdomen was the site of a large opaque density corresponding to the abdominal mass felt on physical examination (fig 1, A)

The retrograde studies showed obvious medial displacement of the upper right ureter and distortion of the right renal pelvis and calyces The left kidney again appeared normal (fig 1, *B*)

Aortography had to be done three different times before satisfactory films were obtained The first one was done on a Friday, and the dye was seen to be outside the aorta The next was done the following Monday and showed an excellent filling of the celiac axis, especially the splenic artery, so aortography was repeated two days later and what were felt to be excellent diagnostic films were finally obtained These films were thought to be rather typical of a large renal cyst The aorta was displaced far to the left and thus may be the explanation for the difficulty in obtaining satisfactory films the first two times (fig 1, C)

Presacral oxygen insufflation after the method of Ruiz Rivas was done prior to the first aortography but none of the oxygen ever dissected its way around the right renal mass (We have found, as have others,[3] that large retroperitoneal masses seal off the retroperitoneal fascial planes, thus preventing the diffusion of oxygen around them) This procedure caused the patient considerable abdominal and back pain and was not repeated The preoperative diagnosis was 'huge cyst of the right kidney with medial displacement of the kidney and ureter and no function of this kidney "

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Operation: The patient was in the left lateral decubitus position and the usual kidney incision was made. The presenting portion of the mass was exposed extraperitoneally without any difficulty and was smooth and cystic to palpation. It had a thick capsule, green in color. A trocar was inserted, and only about 450 cc of dark brownish fluid could be aspirated. The cyst would not collapse. It was felt that it might be multiloculated and so it was opened between guy sutures. The interior was filled with a large amount of greenish crumbly material something like dry oatmeal. No more fluid was visible.

Since the cyst would not collapse by aspiration, it was decided to remove it in toto, together with the nonfunctioning kidney. The twelfth rib was therefore resected without incident and the mass was freed by sharp and blunt dissection. Bleeding was moderate and was controlled with hot packs. When the mass was finally shelled out, the ureter having previously been ligated and sectioned, it was seen that the kidney was lying in its bed, split wide open as a book would be opened in the middle, and still attached to the renal pedicle.

The split open kidney was bleeding moderately, and this was easily controlled by manual compression of the pedicle. The pedicle was then clamped, cut, and suture-ligated, the kidney being removed without difficulty. After a Gelfoam sponge had been placed at the site of the upper pole and right adrenal gland where there was some oozing, two Penrose drains were inserted and the wound closed in layers. The patient received 1500 cc blood during and immediately after the operation and was returned to the ward in satisfactory condition.

Pathologic report (Perry Hough, M.D.): The specimen consisted of a glob-

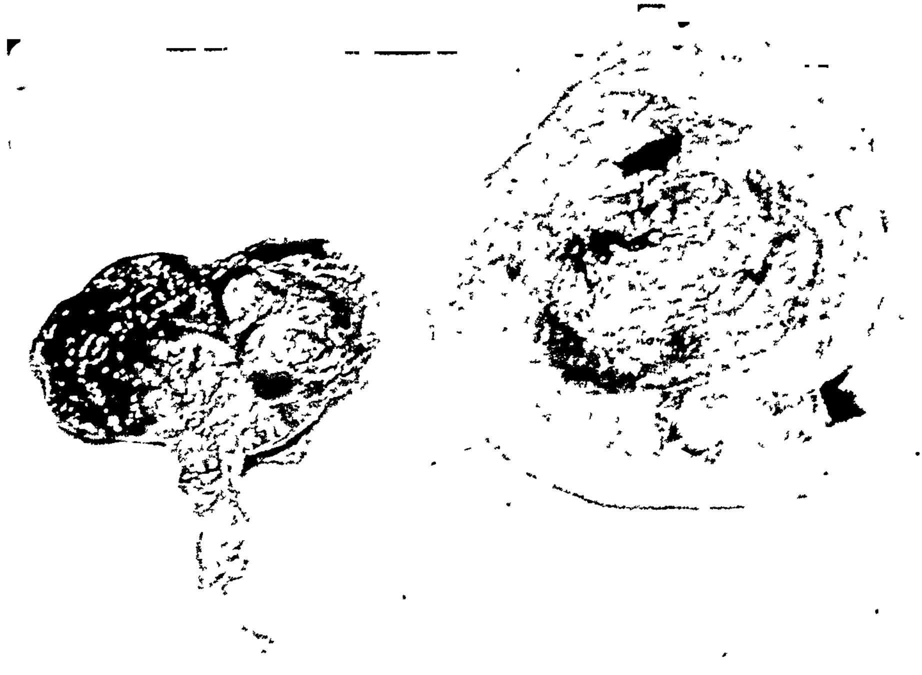

FIG. 2. Gross specimen tumor, and kidney split open from pole to pole in delivering what was thought to be huge cyst.

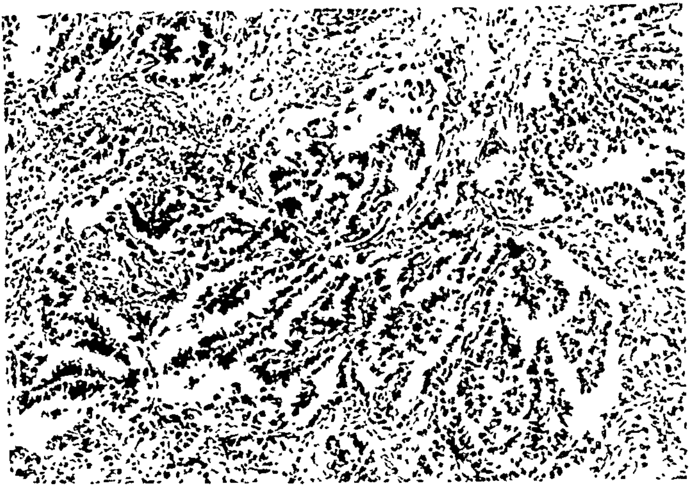

FIG 3. Microscopic section showing papillary adenocarcinoma

ular, encapsulated, partially collapsed mass of completely necrotic tumor 28 cm. in diameter. The adherent fat was infiltrated by tumor. Separately received was a kidney split open from pole to pole, revealing a hydronephrotic pelvis of moderate degree and attached 8–10 cm. of normal looking ureter. Beneath the pelvic mucosa were found masses of soft grey tumor (fig. 2).

Microscopically the tumor tissue was composed of cuboidal or lower columnar cells forming irregular glandular acini with a papillary arrangement. Anaplasia and mitoses were 2 plus. Areas of necrosis were present. The large central necrotic mass was composed mostly of old blood. Diagnosis: Papillary adenocarcinoma of the kidney, grade 2 (fig. 3).

Postoperative course was uneventful as far as vital signs and wound healing were concerned. The patient had a loose rattling cough, quite persistent, and physical examination showed scattered moist rales bilaterally, but there was no hemoptysis and no chest pain. The sputum was greenish yellow. The patient had a chest x-ray 5 days postoperatively and this showed bilateral pulmonary congestion, an arteriosclerotic aorta, and left ventricular hypertrophy. Because the cough, expectoration and rales persisted, chest x-ray was repeated October 6, 1952 (17 days postoperative) and sputum was sent for acid fast studies. The patient was ready for discharge at this time except for his cough. The chest x-ray now showed, however, extensive infiltration of the left upper and left lower lobes, with fibrotic tuberculous changes in the right upper lobe as well as pneumonitis of the left lung with underlying bronchiectasis. Reactivated tuberculosis was suspected by the roentgenologist. On this same day, sputum was positive for acid fast bacilli, and the patient was transferred to the tuberculosis isolation unit of the hospital where streptomycin and PAS therapy were begun.

Six weeks postoperatively the patient said he was feeling fine, had no urinary symptoms, wound healed completely, cough practically gone and he wanted to go home, but almost every other sputum examination was positive for tuberculosis. He therefore had to follow the tuberculosis regimen of the State of Connecticut and was awaiting transfer to a sanatorium for long term care. Arrangements were made for him to receive radiation therapy to the site of the carcinoma and this was accomplished 6 weeks postoperatively, after which the patient was transferred to the Cedarcrest Sanatorium for treatment of his pulmonary tuberculosis. He finally died of disseminated carcinomatosis in February 1953, at Cedarcrest, proven by autopsy.

SUMMARY AND CONCLUSIONS

A 61 year old white man with a huge mass of the right kidney was subjected to complete urologic investigation, including aortography. A diagnosis of renal cyst was made on the basis of the above workup, especially because of the paucity of blood vessels supplying this mass.

At surgery, the mass was found to be an encapsulated papillary adenocarcinoma of the kidney, grade 2, with adherent fat infiltrated by tumor, as well as tumor beneath the pelvic mucosa.

We believe that because of the extensive and rapid growth of the tumor, massive necrosis and hemorrhage ensued, with lack of blood supply causing renal arteriography to give the appearance of renal cyst rather than neoplasm.

We feel that any patient with an abdominal mass should have excretory and/or retrograde urography to rule out urological disease.

Finally, when there is a space occupying lesion in the kidney, one should still adhere to that time tested phrase, "tumor of the kidney, cyst or neoplasm," and exploration is indicated.

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SPONTANEOUS RUPTURE OF RENAL PELVIS SECONDARY TO A SMALL URETERAL CALCULUS

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Since Wunderlich,[1] in 1856, first described "spontaneous apoplexy of the renal capsule," spontaneous rupture of the kidney has been the subject of clinical reports at irregular intervals. Speese[2] in 1913, and Henline in 1924[3] were able to collect twenty-one and 24 cases respectively. In 1949 Potampa[4] resurveyed the literature and added 2 cases to bring the total to thirty-nine. In addition, the topic has been discussed by Abeshouse,[5] Mathé,[6] Lorenz,[7] and others.

Lowsley and Kirwin[8] state that "some form of renal disease which weakens the walls of the kidney or renal pelvis is a prerequisite to spontaneous rupture," and include as reported causative factors hydronephrosis, lithiasis, tuberculosis, abscess, tumors, and arteriosclerosis. Rupture due to an impacted calculus, however, is exceedingly rare.[9] Abeshouse[5] in his exhaustive article of both traumatic and spontaneous rupture cites nine instances of ureteral calculus and three of impacted stones at the ureteropelvic junction. Salvin,[10] however, in surveying those instances of rupture without trauma secondary to ureteral calculi was able to find but four instances in the literature and added a fifth case.

The occurrence of a case of spontaneous rupture secondary to a small ureteral calculus which was demonstrated by excretory urography, and which was treated conservatively without surgical intervention and with complete recovery of the patient, prompted this report.

CASE REPORT

C. M., U. H. 282-900. A 55 year old white man entered the hospital with the chief complaint of left flank pain radiating to the testicle of 24 hours' duration. The pain was colicky in nature and associated with nausea, but no vomiting. The present illness began at noon of the day prior to admission, when the patient was suddenly seized with severe pain in the left flank. He was seen by his local physician who gave him some morphine with temporary relief, but the pain recurred at irregular intervals until the time of admission. Although there

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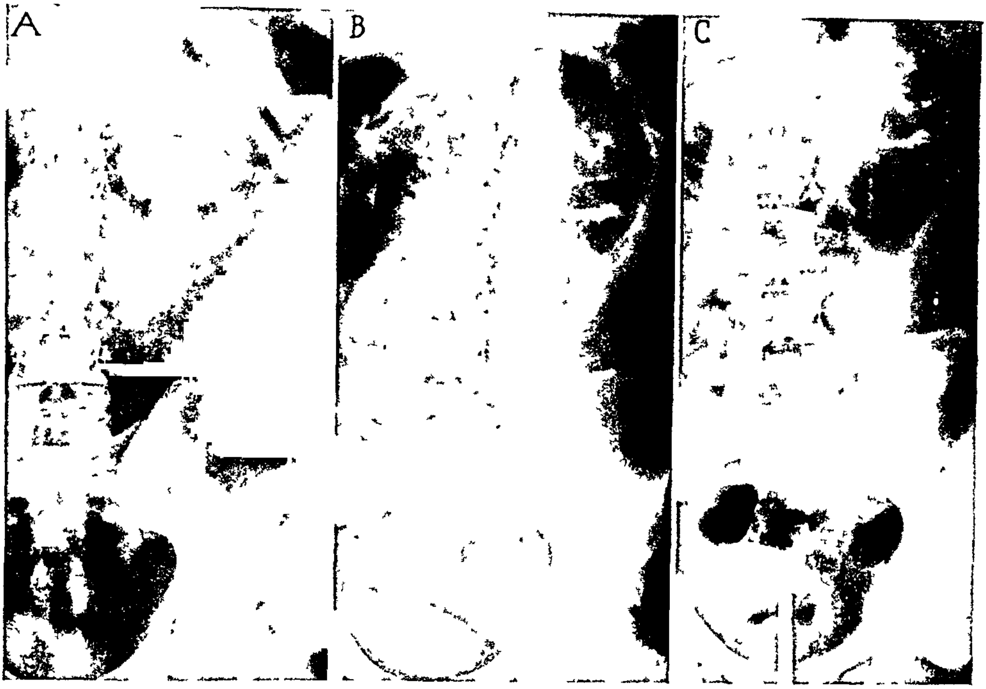

FIG. 1. *A*, plain film showing small calcific density slightly below region of left uretero-pelvic junction. *B*, thirty minute film demonstrating wide extravasation. *C*, retrograde ureteropyelogram made day following excretory urograms showing no evidence of extravasation

was slight dysuria, hematuria was not noted. From the onset of pain the patient was nauseated until admission 24 hours later. Family history and past history were noncontributory. There had been no previous episode of renal colic.

Physical examination revealed a well developed, well nourished male in mild distress. His skin was pale and cool. Temperature was 37.7, pulse 80, respirations 20. Blood pressure was 125/60. Positive physical findings were confined to the back where there was moderate left costovertebral angle tenderness without spasm. There was no abdominal tenderness or spasm. Laboratory data revealed completely clear urine without cells, hemoglobin of 14 grams, and white blood count of 13,200.

The patient had several attacks of colic during the night of admission, which were relieved by narcotics. The plain x-ray (fig. 1, *A*) showed a small calcified shadow suggestive of a calculus in the region of the left ureter below the ureteropelvic junction. The right intravenous pyelograms were completely normal. However, on the left, the intravenous pyelogram, beginning with the ten minute film and increasing up to the 40 minute film, showed definite extravasation of the contrast material (fig. 1, *B*). In a subsequent film taken several hours later, the contrast material had puddled along the psoas shadow.

Following pyelography the patient's temperature, which had previously been normal, rose to 39.5° by 4 p.m. and cystoscopy was undertaken to establish a definite diagnosis and to institute proper drainage of urine if possible. At cystoscopy clear efflux of urine was noted from both ureteral orifices. All attempts to catheterize the left ureter met an obstruction at 1.0 cm. Retrograde injection from this point revealed a normal ureter up to the suspected calculus. The contrast material did not flow past the calculus. The patient was returned to the ward and placed on penicillin. *The temperature fell overnight to 38.5°*, and the patient had a comfortable night. There was only slight tenderness in the flank. Cystoscopy again was carried out the next morning and it was still impossible to catheterize the left ureter for more than 1.0 cm. Ureteropyelograms, however, were satisfactory and revealed the previously noted shadow to be a small calculus, 2 by 5 mm., just below the ureteropelvic junction. This time the opaque solution flowed beyond the calculus and a normal pyelogram was obtained. *No extravasation could be demonstrated (fig. 1, C).*

The patient's temperature returned to normal within 24 hours. The leukocyte count fell to 9,800 by the third hospital day. Excretory urography on the sixth hospital day revealed no obstruction, extravasation, or hydronephrosis, and showed only slight descent of the stone. The patient was discharged on the tenth hospital day, and simply kept under observation for 1 month during which time he had no symptoms whatsoever. The excretory urograms were repeated, and again revealed but slight descent of the stone with no obstruction above it. Cystoscopy was also carried out with ureteral catheterization, and no obstruction of the left ureter was demonstrated below the stone.

The patient was re-admitted three, six and nine months after the onset of his illness. He had no urinary symptoms between studies and never any evidence of infection until his last admission when a brief episode of colic preceded his re-entrance into the hospital. Pyelograms, on each occasion, revealed the gradual spontaneous downward passage of the calculus until extraction was possible by means of the Johnson basket, nine months after the initial episode. Retrograde studies at no time showed obstruction, or a distorted pelviocalyceal system. Since removal of the calculus, he has been followed for three years with no evidence of recurrent stone formation, obstruction, or extravasation.

DISCUSSION

Rupture of the kidney occurring without trauma has been categorized by Mathé[11] into two types: a) rupture of the parenchyma with hemorrhage, and b) rupture of the pelvis with extravasation. There is no question of the necessity for surgical intervention in the former case, and the consensus[9, 11] is that it is necessary in the latter instance. However, in this case because of the free efflux of urine from both ureteral orifices, because of the paucity of physical findings and because of the absence of infection it was decided to treat the patient conservatively. The fortunate outcome was indubitably due to several factors, not the least of which was *the efficacy of the chemotherapeutic agents employed.* If fever or leukocytosis had persisted, ureterolithotomy with drainage would have been employed.

The small size of the stone, an equally important factor in the ultimate fortunate outcome was a determining factor in the program of nonintervention. The failure of the stone to pass immediately, however, was discouraging, and only the repeated retrograde and intravenous pyelograms which showed no extravasation, obstruction, or hydronephrosis, and the patient's extreme reliability and co-operation permitted his temporary discharge and ambulatory observation.

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SUMMARY

A case of spontaneous rupture of the renal pelvis due to an impacted small ureteral calculus, treated conservatively with spontaneous recovery, and with ultimate extraction of the calculus, is reported.

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ACUTE RENAL TRAUMA IN BOXERS

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Professional boxing has been cited as the nation's most dangerous trade.[1] In recent years the attention of the medical profession has been focused upon the boxing industry in an effort to reduce to a minimum the inevitable trauma and the attendant after effects received by its participants.[2]

Brain injuries are the most serious and most dramatic accidents which occur, and the literature is replete with encephalographic studies, for the development of the highly technical instrument and the specialized training necessary for the interpretation of its records have made the detection of brain trauma a feasible procedure.

No such expensive and highly technical apparatus is needed for the detection of trauma to the kidneys; a routine urinalysis will suffice. In spite of this ease of assay, there is no previous study reported in the literature to date on the changes that occur in the urine of boxers following a bout.

The material for this study was obtained with the co-operation of the New York State Athletic Commission and professional boxers who fought at the Madison Square Garden and at St. Nicholas Arena in New York City during the years 1952 and 1953.

In studying the changes that occur in a man's urine after he has engaged in a boxing match, it is necessary to consider not only the factor of trauma, but also that of strenuous exercise, for it is with both factors with which we are dealing, and the effects of the latter should not be confused with those due to the constant raining of blows to the kidney region during a fight. A preliminary brief consideration of the effects of strenuous exercise on the urine is therefore in order. That urinary changes do occur following muscular exercise is a fact well chronicled in the world's physiological literature.

Following exercise there is a decrease in the urine volume. The renal plasma flow and filtration rate have been shown to be reduced markedly during exercise, the more intensive the exercise the greater the effect, thus making this blood available for circulation in active regions of the body.[3, 4, 5, 6, 7, 8]

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[8] Barclay, J. A., Cooke, W. T., Kenney, R. A. and Nutt, M. E.: The effects of water diuresis and exercise on the volume and composition of the urine. Am. J. Physiol., **148:** 327, 1947.

If the exercise is severe, it may be accompanied by albuminuria. That protein appears in the urine after strenuous exercise is interpreted as indicating that exercise induces a generalized vasoconstriction and at maximal exercise levels a large number of glomeruli drop out of function and suffer ischemia to the extent that they begin to leak protein. Erythrocytes and casts have not been reported to be found in the urine due to the effects of exercise alone.

Following exercise there is a decrease in the chloride concentration in the urine and an increase in the urinary acidity, ammonia and phosphate.[9, 10] The fall in chloride concentration may be due to the loss of chloride in the sweat and the shift of chloride from the blood into the active muscles. The rise in acidity of the urine is explained by the increased acid excretion. It has been shown that a large quantity of lactic acid may be found in the urine after short periods of severe exercise. With this excretion of acid there is an increase in the ammonia output in an effort to save base. The kidney in addition to the production of ammonia has another mechanism for the conservation of base. There is a slight increase in the phosphate excretion and the ratio of the disodium to the mono-sodium phosphate varies with the change in the hydrogen ion concentration of the urine. Since this change is in favor of the mono-sodium phosphate, base is thereby saved.

METHOD

This study was made on a group of 139 professional boxers. Of these, the comparison of urinary findings before and after a bout was made in 103; in the other 36 cases, specimens were obtained only before the fight and not afterward because either the scheduled bout did not take place, or as was the case in five instances, the boxer could not urinate immediately after the match.

A freshly voided specimen of urine was collected from each boxer on the day of the fight while he was undergoing the routine pre-fight examination in the Medical Office of the New York State Athletic Commission.

The "before" specimens were analyzed within an hour after their collection.

It is a routine procedure for a boxer to urinate before leaving his dressing room immediately before a fight.

While the bout was in progress an attempted estimate was made of the amount and severity of blows received in the region of the kidneys and a tabulation was made of the number of rounds the fight lasted.

Back in the dressing room approximately 5 to 20 minutes after the fight, another voided specimen was collected from each boxer, and these specimens were likewise analyzed within an hour of the time of their collection. The specimens were analyzed in exactly the same manner so as to obtain results which were comparable.

Each urine specimen was examined for color, turbidity, specific gravity, pH, glucose, albumin, and acetone. A well mixed sample of each was centrifuged and

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a detailed microscopic examination of the sediment was performed, the final results being recorded under the high power objective

SUMMARY OF RESULTS

It was found that 46 per cent of the fighters' urines changed from clear before the bout to turbid immediately afterwards The urinary specific gravity increased in 80 per cent of the cases Traces of acetone were manifest in 14 per cent The urinary pH decreased in 39 per cent Sugar was spilled in the urine in 9 per cent of the boxers Albuminuria, which was not present before the bout, was present in 68 per cent of the boxers after the fight

Microscopically, red blood cells were found in significant pathological amount in 73 per cent of the boxers after fighting, and 26 per cent were found to have casts of granular or hyaline variety in their urine In each case, when casts were present, red cells were also present microscopically.

Small numbers of crystals, mostly calcium oxalate, were seen in 20 per cent of the boxers' urines

The data obtained from the urinalysis were broken down further in an attempt at correlating the severity of urinary changes noted after the bout with such factors as the number of rounds fought, the estimated severity of blows to the kidney region, the weight and over all protective muscle mass of the boxer, but the only factor that seemed to correlate was the number of rounds the fight lasted

For example, 65 per cent of those who fought 1–6 rounds had hematuria, while 89 per cent of those fighting 7–12 rounds had hematuria, the number of red cells present being much greater in the latter group, of whom four had total gross hematuria

Similarly albuminuria was present in 60 per cent of those who fought 1–6 rounds, and in 87 per cent of those who fought 7–12 rounds

CONCLUSION

Actually, we have proved the obvious, namely, that in addition to an effect of exercise, there is also an effect of acute trauma observed in the urine of boxers immediately after a fight, and that the degree of severity of changes noted correlates with the duration of the fight which in turn has a bearing on the amount of renal trauma

These fighters experience acute trauma to the kidneys evidenced by the finding of a high percentage of albumin, red blood cells and casts in the urine Exercise alone will *not* produce these changes

It is not within the scope of this paper to arrive at any conclusions as to the long range effect of the acute renal trauma experienced during the course of repeated boxing matches The door is open for further investigation into this interesting problem

This investigation should include repeated urinalyses, so that the duration of these abnormal findings may be ascertained This was attempted in our study, but, without official sanction, it was impossible to get these boxers to report back for daily follow-up studies. This should be the next step.

The question of the effect of repeated trauma on the production of scarring in the kidneys and eventual diminution of renal function should be studied. Perhaps this might best be done at present on the group of men who have grown too old to fight in the ring, and who are now retired from boxing.

It is our impression from this study that a routine urinalysis should be part of each pre-fight examination, rather than its being done just the first time a fighter is examined for license. Until further information is obtained, we recommend that a boxer not be allowed to fight until his urinary findings have returned to normal.

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WAR INJURIES OF THE UPPER URINARY TRACT

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USS Repose (AH-16)

This paper is intended as a symposium on injuries of the upper urinary tract, caused by the implements of war, as seen in the United States Naval Hospital in the U.S.S. Repose (AH-16) during its stay in Inchon, Korea, from June 1952, to January 1953.

The only cases to be considered are those which have been treated per primam in this hospital. It will not include cases sent to us from Marine Medical Companies for postoperative care.

In order to give the reader a clear idea of the type of casualties received, some background data are indicated. Our hospital ship, during its stay in Inchon, supported the 1st Marine Division and Korean Marines. We were within twenty minutes' helicopter distance from the MLR (main line of resistance). All casualties seen by us were given first aid by Battalion Aid Stations and Marine Medical Companies prior to their arrival here.

The diagnosis of injury to the genito-urinary tract is not difficult. The salient points to be remembered are wound of entrance (and exit, if present), course of missile, presence of hematuria, and symptoms and signs of acute abdomen caused either by the injury to the genito-urinary tract or by injury to other abdominal organs. The diagnosis of injuries of the penis, scrotum, testicles and urethra is obvious. The methods of diagnosis will be discussed further with each particular group of injuries. The urologist should not hesitate to use cystoscopy, excretory urography, etc., whenever they are deemed necessary. There are few actual contra-indications to cystoscopy and retrograde pyelography. If a patient is not in shock, and diagnosis is in question, cystoscopy may save the surgeon considerable work at the time of operation or may save the patient a second procedure at a later date. The latter is particularly true when injury to the ureter is suspected, e.g. we have performed cystoscopy on a patient in bed, in the presence of a hip spica cast to determine whether a ureter had been injured, since a large metallic foreign body was lying on the psoas muscle along the course of the ureter, and the total urine output had decreased since injury.

It is important to remember that injuries of the upper genito-urinary tract (ureters and kidney) are more than likely to be associated with injuries of other abdominal viscera. This necessitates a complete abdominal exploratory in almost every case to determine the extent of injury and will undoubtedly save more lives than any other single procedure carried out on the patient. This fact will be made more clear in the remainder of this paper.

INJURIES OF THE KIDNEY

A number of classifications of renal trauma have been proposed in the literature. Some consist of describing the actual lesions seen in the kidney such as

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TABLE 1. *Injuries of the kidney*

CASE	WOUND ENTRANCE	*CLINICAL FINDINGS*	CONDITION OF PATIENT PREOP.	INCISION FOR EXPLORATORY	GU TRACT INJURIES	ASSOC. VISCERAL INJURIES	OP. TREATMENT FOR GU INJURY	CONDITION POSTOP.
1	Rt. flank	Hematuria, *acute* abdomen	Good	Rt. transverse abdominal	Contusion of rt. kidney	Contusion of hepatic flexure of colon	Rt. retroperitoneal space drained	Good
2	Lt. anter. abdomen	Hematuria, acute abdomen	Fair	Lt. rectus	Small shallow laceration on surface of lt. kidney	Penetrating wounds of ileum & descending colon	Lt. retroperitoneal space drained	Complications from other injuries with subsequent recovery
3	Multiple wound of lt. ant. abdomen	Hematuria, acute abdomen, lt. flank and lt. CVA tenderness	Shock	Lt. pararectus	Small laceration of upper pole of lt. kidney	Perforating wounds of ileum & jejunum	Lt. retroperitoneal space drained	Good
4	Lat. aspect of rt. lower chest	Hematuria, sucking wound of rt. chest, acute abdomen	Shock	Rt. thoraco-abdominal	Perforating wound of upper pole of rt. kidney	Perforating wound of lower lobe, rt. lung	Suture of kidney wound	Good
5	Rt. infero-lat. chest wall	Hematuria, acute abdomen	Shock	Rt. thoraco-abdominal	Perforating wound of upper lobe, rt. kidney	Perforating wound of lower lobe, rt. lung; laceration of rt. lobe of liver	Suture of kidney wound	Good
6	Rt. flank	Hematuria, *acute* abdomen, coma	Shock	Rt. rectus	Rt. kidney split	Laceration of hepatic flexure of colon (see case presentation)	Rt. nephrectomy	Died (cause of death was laceration of rt. cerebral hemisphere)
7	Post. aspect of rt. flank	Hematuria, acute abdomen	Shock	Rt. rectus	Upper half of kidney split	Laceration of rt. lobe of liver; perforating wound of hepatic flexure of colon	Rt. nephrectomy	Good
8	Rt. lower chest anteriorly	Hematuria, acute abdomen	Shock	Rt. thoraco-abdominal	Stellate laceration of central portion of rt. kidney	Perforating wound of lower lobe, rt. lung; laceration of rt. lobe of liver	Rt. nephrectomy	Good
9	Lt. flank	Hematuria	Good	Upper lt. transverse abdominal	Laceration of central portion, lt. kidney	Laceration of spleen	Lt. nephrectomy	Good

laceration, contusion, etc , and others group various types of lesions into three categories I minor, II major, III critical Minor includes those injuries causing parenchymal damage without rupture of capsule or extension into pelvis, major includes parenchymal damage and capsular rupture with almost invariable extension into pelvis and calyces, and critical includes extension of lesion to vessels of renal pedicle

For the sake of practicality, the types of renal injuries to be presented will be grouped according to the treatment which was required and carried out (table 1)

Type I Injuries requiring no direct treatment These include contusions of the kidney, caused by a blow on the outside, or by the force of a missile passing close to the kidney, or by a missile lightly striking the kidney, and small laceration of renal capsule and outer cortex where on exploration the bleeding has stopped and the kidney appears undamaged otherwise

Clinically, there is usually microscopic hematuria and occasionally gross hematuria, pain in the involved flank or costovertebral angle with splinting of the adjacent muscles, and evidence of a blow or a wound in or near the involved region If there is associated injury to abdominal viscera, there will be symptoms and signs of an acute abdomen Shock will be present only if other organs, etc , have been damaged severely In some cases, there is associated chest injury which may or may not require a thoracotomy If the latter is carried out, it will be easy to determine whether or not the missile could possibly have struck the kidney, an uninjured diaphragm and the absence of signs of abdominal injury will usually obviate the necessity of further abdominal and retroperitoneal exploration In rare cases, the kidney can be ruptured by a proximal blow This will, of course, produce symptoms which will make one suspect such a condition

If there is no associated injury to abdominal viscera, making an exploratory laparotomy unnecessary, retrograde pyelograms should be done to determine the extent of renal injury This will reveal intact pelvis and calyces

In every case of abdominal injury the renal areas should be palpated and observed as part of the laparotomy If the missile has perforated the posterior peritoneal wall, the retroperitoneal space should be explored In this way the kidney and adjoining structures can be visualized to determine whether or not they have been injured In cases where it is necessary to explore the retroperitoneal space, it is oftimes necessary to drain the area

One finds that in these types of cases the hematuria will usually disappear or become less within 72 hours The kidney should function normally and no complications should develop from the renal injury

Case 1 A 21 year old U S Marine was hit by enemy mortar fire sustaining wounds of right flank, arms and both lower extremities Examination revealed blood pressure 120/60, rigid abdomen with tenderness throughout but more marked on right, and multiple wounds of extremities Catheterized urine specimen was grossly bloody X-ray of abdomen revealed two intra-abdominal metallic foreign bodies in the right upper quadrant

An exploratory laparotomy was carried out through a right transverse incision A contusion of the hepatic flexure of colon was noted along with a contusion of the retroperitoneal wall overlying the right kidney. The retroperitoneal space was free of blood and the renal cortex was intact. The right retroperitoneal space was drained and the wound closed in the usual manner. Other wounds were adequately debrided.

Postoperatively, the urine contained blood for 36 hours, then completely cleared. Right flank tenderness persisted for 7 days. Patient did well otherwise.

Case 2: A 28 year old U. S. Marine was hit by enemy mortar fire sustaining wounds of left side of abdomen and neck. On examination blood pressure was 116/82, abdomen was rigid and acutely tender throughout, and there was slight tenderness in the left costovertebral angle. The urine was grossly bloody.

Exploratory laparotomy was carried out through a left rectus incision. There were penetrating wounds of the descending colon and ileum. Upon exploration of the left retroperitoneal space, a small shallow laceration was observed on the anterior surface of the kidney. The latter was no longer bleeding and the remainder of the kidney was intact. The retroperitoneal space was drained through a stab wound; perforations of the ileum were sutured, and a colostomy was carried out through stab wounds. The missile was removed from the neck and wounds were debrided and drained.

Urine was free of blood one day postoperatively. The patient had other complications as a result of other injuries, but this is beyond the scope of this paper.

Case 3: A 22 year old U. S. Marine hit by enemy mortar fire sustained multiple wounds of the abdomen. Patient was in mild shock when brought into one of the forward medical companies. He was given blood and sent here by helicopter. On admission, his blood pressure was 105/72. Examination revealed wounds of extrance on the left lateral aspect of the abdomen at the level of the umbilicus. There was marked rigidity and tenderness of entire abdomen. The left flank and the left costovertebral angle were also markedly tender. The urine was grossly bloody.

An exploratory laparotomy was carried out through a left pararectus incision. There were multiple perforations of the ileum and the jejunum which were sutured primarily. A small hematoma was present in the left retroperitoneal space with perforation of the retroperitoneal wall near the upper pole of the left kidney. There was a small laceration of the upper pole of the kidney. The bleeding had stopped and the remainder of kidney was unharmed. No direct treatment was given to the kidney. The retroperitoneal space was drained through a stab wound in the left flank. The left colic gutter was drained and the abdomen closed in the usual fashion.

The postoperative course was uneventful with the exception of ileus which was easily handled with intubation. The urine remained loaded with red blood cells and white blood cells for 4 days after which it cleared considerably. By the time the patient was evacuated, the urine contained only a few white blood cells and red blood cells. His condition was good.

Type II. Injuries of kidney necessitating repair. These include injuries of renal substance in which repair is possible by means of simple suturing, partial nephrectomy, or other procedures. Injuries of this sort can be minimal or severe.

They can include a laceration of renal cortex in which suture of renal substance is required for hemostasis, a laceration or perforation of renal substance with extension into calyx in which accurate suture of laceration including calyceal tear is necessary not only for hemostasis but to prevent subsequent fistula formation, and severe damage to upper or lower pole of kidney in which a partial nephrectomy is necessary to save the remainder of the kidney

The diagnosis will be suspected upon noting the wound of entrance and course of missile The clinical picture of such an injury varies with the extent of damage *The patient will almost invariably have hematuria, he may or may not be in* shock, he will have flank and costovertebral angle tenderness, a retroperitoneal mass may be palpated or visualized on plain x-ray, signs of an acute abdomen may be present, and urography will show extravasation of dye, if the injury has included the calyceal system In the majority of instances an associated injury to other abdominal viscera will be present, and symptoms and signs of an acute abdomen will prevail Associated injury to thoracic structures is not uncommon, the clinical picture characteristic of such an injury will of course present itself

Case 4 A 24 year old Korean Marine was hit by enemy grenade fragments, sustaining wounds of the right lower chest and the right side of the abdomen The urine was grossly bloody Examination revealed a sucking wound of the right lower chest (lateral) with diminished breath sounds in the right chest, the mediastinum was shifted slightly to the left There was a small wound in the right lower quadrant of the abdomen The abdomen was rigid and acutely tender Patient was in shock when brought in by helicopter He required 1000 cc whole blood prior to surgery

X rays revealed missiles in the right retroperitoneal area near the upper pole of the right kidney

The patient was explored through a right thoraco-abdominal incision A wound of the lower lobe of right lung was found sealed There was a perforating wound of the upper pole of the right kidney which was bleeding freely Hemostasis was established by means of interrupted mattress sutures tied over pieces of fat A laceration of the right lobe of the liver was sutured with interrupted mattress sutures of ribbon catgut The retroperitoneal area was drained through a stab wound, the liver area was drained through the incision A thoracostomy tube was left in the chest

The postoperative course was entirely satisfactory The retroperitoneal drain was removed 5 days postoperatively, and the thoracostomy tube was removed in 48 hours The abdominal drain was removed in 8 days because of bile drainage The chest was clear by x-ray 8 days postoperatively Tenderness in right upper quadrant persisted up to the time of evacuation There was no bile drainage, and the urine was clear

Case 5 A 27 year old Korean Marine hit by grenade fragments sustained wounds of right arm, right lower extremity and right flank Patient was sent to this hospital by helicopter

Examination revealed patient to be in shock, blood pressure 60/20, pulse 90 and very thready; wounds of right upper arm, right knee, and right inferolateral chest. The abdomen was rigid and tender. The urine was grossly bloody.

The patient was given blood on admission to combat shock. When his condition permitted, patient was taken to the operating room and explored through a right thoraco-abdominal incision. The right chest was emptied of blood; a small wound of the lower lobe of right lung needed no suturing as it had sealed. A small perforation was present in the right leaf of diaphragm. The right lobe of the liver had a laceration about 7 cm. long extending from the superior to inferior surface. This was sutured interruptedly with ribbon catgut. There was a retroperitoneal hemorrhage in the region of the right kidney. Exploration of this area revealed a through and through perforation of the upper pole of the right kidney. This was repaired by mattress sutures taken over a piece of muscle. Penicillin, 300,000 units and 0.5 gm. streptomycin were placed in the chest. Drains were placed retroperitoneally and under liver. A tube was left in the chest. Closure was carried out in the usual manner. The other wounds were debrided.

Postoperatively, the patient did well. He voided clear urine on the third postoperative day. The thorocostomy tube was removed on the third day. All drains were removed ten days postoperative. Cystoscopy was performed 25 days postoperative and retrograde studies were carried out. The right kidney appeared normal with good function. The patient was evacuated for further convalescence.

Type III. Injuries of kidney necessitating nephrectomy. A policy of conservatism was carried out with regard to nephrectomy for the treatment of kidney injuries. The conservation of renal tissue was of prime consideration in every case of severe kidney injury. In cases where kidney injury was observed, the presence of the contralateral kidney was always checked; in this manner it was possible to estimate whether or not that kidney was normal in size and consistency. In this series, nephrectomy was carried out in those cases in which the kidney was damaged beyond repair, and where it was necessary to tie off the renal pedicle to stop the hemorrhage. There was no difficulty in determining whether a kidney was beyond repair. In these cases the kidney was severely lacerated, enclosed in a massive hematoma, and was bleeding profusely.

It will be seen that the cases to be presented below are all surgical emergencies. Shock was present in almost every case, as was gross hematuria and the findings of an acute abdomen. In four of the five cases there was associated injury to other abdominal viscera; in one there was associated injury to intrathoracic viscera. A retroperitoneal mass was present in every case but could not be palpated because of the extremely rigid abdomen. These patients invariably received blood at a medical company before reaching this hospital.

Diagnostic studies were unnecessary in these cases as they were treated as emergencies. Exploratory procedures were carried out as soon as patient's condition would permit.

Case 6: A 22 year old Marine hit by enemy grenade fragments sustained wounds of the right flank and bridge of nose. Upon arrival, his blood pressure was 80/60. His abdomen was rigid, urine was grossly bloody, and he was bleeding profusely from a wound of his face. The patient was in coma, and his condition was critical. After receiving two pints of blood, his pressure rose to 92/68. An abdominal exploratory was carried out through a right rectus incision. The peritoneal cavity was full of blood. The hepatic flexure of colon was raggedly lacerated. A massive retroperitoneal hematoma was present on the right. The retroperitoneal wall was incised and renal area exposed. The right kidney was enclosed in the hematoma. The kidney was found split in its central portion. In attempting to further visualize kidney, a profuse hemorrhage was started. After clamping the pedicle, the hemorrhage was controlled. The pedicle was cut and tied, and the kidney removed; however, the blood pressure had dropped once more and patient expired on the operating table.

Postmortem examination revealed, in addition to the aforementioned findings, a lacerated right cerebral hemisphere caused by the missile which entered through the nose and lodged in the occipital bone after traversing the brain.

Case 7: A 19 year old private, USA, hit by enemy shrapnel sustained wound of the right side of the abdomen in the region of the mid flank. The wound of exit was posterior to wound of entrance. Examination of abdomen revealed it to be rigid and tender throughout. A catheterized urine specimen was grossly bloody. Stomach aspirations were negative. X-ray revealed a large metallic foreign body lodged in the anterior abdominal wall, and the wound of entrance to be posterior. The patient received 3 units of whole blood. The blood pressure was 120/70 at the time of surgery; he had been in shock when he was received by the forward medical company. The patient was brought to the ship by helicopter in satisfactory condition.

The patient was explored through a right rectus incision. Blood and fecal material welled up from within the peritoneal cavity. A large rent was seen in the retroperitoneal wall on the right. There was a profuse hemorrhage coming from the retroperitoneal space. The kidney was isolated and pedicle clamped and tied. The kidney was then removed. Its upper half was found split. A small laceration in the right lobe of the liver was repaired with ribbon catgut sutures. A perforation of the hepatic flexure of colon was repaired and an ascending colostomy was carried out, between Kocher clamps, in the center of the abdominal incision. The metallic foreign body was removed. Wide debridement and drainage of the retroperitoneal space and peritoneal cavity was carried out.

The patient tolerated surgery well. His postoperative condition was satisfactory. Prognosis is excellent.

Case 8: A 22 year old corporal, USMC, shot by sniper sustained bullet wounds of right chest and abdomen. The bullet entered at the level of the ninth rib anteriorly; exit was at the level of the twelfth rib posteriorly. The patient had no dyspnea or cough. The right side of the abdomen was extremely tender. There was muscle guarding and abdominal rigidity throughout. Voided urine was grossly bloody.

The patient was taken to a forward medical company in shock. He was given 2 pints of blood and antibiotics. X-ray studies revealed the right diaphragm to be slightly higher than normal. He was sent here by helicopter. Upon admission, the blood pressure was 130/70.

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The patient was taken to a forward medical company in shock He was given 2 pints of blood and antibiotics X-ray studies revealed the right diaphragm to be slightly higher than normal He was sent here by helicopter Upon admission, the blood pressure was 130/70

Through a right thoraco-abdominal incision the right chest, abdomen and retroperitoneal space were explored. There was a small hole in the lower lobe of the right lung which had sealed. A small hole was present in the right leaf of the diaphragm. This was sealed. A large laceration splitting the right lobe of liver was sutured interruptedly with ribbon catgut. There was a massive retroperitoneal hematoma surrounding and including the right kidney. There was a large stellate laceration of the central portion of right kidney. The renal pedicle was isolated, clamped, cut and tied. The right kidney was removed. The retroperitoneal space and bed of the liver were drained. The thoraco-abdominal incision was closed in the usual manner.

The postoperative course was uneventful except for beginning wound dehiscence in the upper portion of abdominal incision. This was closed with steel retention sutures under local anesthesia. Recovery is now progressing favorably at a hospital in the U.S.A.

Case 9: A 20 year old Korean Marine hit by mortar fragments sustained multiple wounds of the right side of the abdomen, extremities and left flank. His entire abdomen was tender and rigid. The urine was grossly bloody.

The patient was explored through a right rectus incision. No pathological process was noted in the right side of abdomen. Blood was seen coming from the left upper quadrant. A left transverse incision was carried out in addition. A lacerated spleen was found and removed The left retroperitoneal area was explored as a hematoma was present in that space. The kidney was found to be lacerated with bone fragments imbedded in its central portion. The renal capsule was stripped by the hemorrhage. As it was felt that a functional kidney could not be salvaged, a left nephrectomy was carried out after first isolating the pedicle so it could be clamped, cut and tied.

The retroperitoneal space was drained through a stab wound.

Recovery was uneventful.

Case 10: A 21 year old Korean Marine hit by enemy mortar fire sustained wounds of the right upper quadrant of the abdomen and right lower chest. The missile entered at level of the eleventh rib and lodged at the level of interspace T-10–11. The patient was taken to a forward medical company in shock. He was given two units of whole blood and sent to this hospital ship by helicopter. Upon examination, his abdomen was rigid with marked right side tenderness. The urine was grossly bloody; his chest was clear. X-ray revealed cloudiness of the right side of the abdomen and the location of missile at interspace of T-10–11.

The patient was explored through a right thoraco-abdominal incision. Intraperitoneal organs were unharmed. A massive hematoma filling the entire right retroperitoneal space was present. The latter was explored and the right kidney was found to be severely lacerated (fig. 1). The pedicle was isolated, clamped, and divided. The kidney was removed with surrounding fascia and adherent hematoma. Most of the clotted blood was evacuated by the handfuls from the retroperitoneal space. The latter was drained through a stab wound. The incision was closed in the usual fashion after the posterior peritoneal wall was sutured.

The patient did well postoperatively. His prognosis is excellent.

FIG. 1. Gross specimen—severely lacerated kidney

Comment: The most important information that can be gained from the preceding discussion is that injury to the kidney by a missile will almost always be accompanied by injury to other organs or viscera. It is the unusual case that will have no associated injury. Numerous postoperative cases sent to us from the forward medical companies in which the kidney had been damaged had in addition associated injury to intraperitoneal viscera, thoracic viscera or both. In view of this, a complete abdominal exploratory is indicated in every case. The severity of thoracic injury can usually be determined by clinical findings, chest x-ray and missile course, and appropriate treatment instituted as necessary.

In upper quadrant injuries of the abdomen where the possibility of liver, spleen or lung injury exists, a thoraco-abdominal incision was preferred. The incision which afforded the best exposure of kidney and adjacent viscera extended from region of umbilicus diagonally upward across the costal cartilages at the level of 7–8 ribs and into the space between those ribs. The diaphragm was split along the line of incision. Repair of the liver, splenectomy, suture of lung, nephrectomy, and complete abdominal exploratory were easily accomplished through such an incision.

In other types of abdominal injuries, a rectus or para median incision was used for the most part. Occasionally, a transverse abdominal incision was carried out, but it was not preferred. Renal exploration was carried out transperitoneally. This has a few advantages over the translumbar approach. The pedicle can be isolated very easily. The injured kidney and hematoma need not be disturbed before the pedicle is clamped, and an abdominal exploratory is more easily accomplished.

INJURIES OF THE URETER

The diagnosis of ureteral injury is usually made after the initial surgery has been done. The ureter is not readily seen during exploratory abdominal procedures unless it is specifically looked for. Ureteral injury then can only be discovered at the time of initial surgery if it is suspected primarily, which necessitates a more through exploration.

In a badly wounded patient, the course and location of the missile on a plain x-ray will be the only clues of a ureteral injury. There may be or may not be blood in the urine. If it is suspected that the course of the ureter has been traversed by the missile, a retroperitoneal exploration should be carried out in that area.

The best and surest method of diagnosis is retrograde urography. This procedure should be done prior to the initial surgery, provided the patient's condition allows such a procedure, and would thereby save the patient a second operation for the repair of his ureteral injury.

The treatment of ureteral injury varies with the extent and location of the trauma. The preferred treatment of a partial tear of the ureter is ureteral intubation with a 10F or 12F ureterostomy tube. In some of these tears, the tube should be brought out with a nephrostomy. In small tears the tube can be coiled in the bladder and removed at cystoscopy. The use of a T tube was attempted for a partial ureteral tear. This will be commented upon below.

In complete severance of the ureter, an anastomosis must be carried out if the kidney is to be preserved in its normal state. Whether or not this can be done depends on how much of the ureter has been injured. If a large section of ureter has been injured so that its ends cannot be approximated without undue tension, an anastomosis will probably be unsuccessful. The treatment of choice in such a case would be nephrectomy, provided the other kidney is normal.

Severed ends of the ureter can be anastomosed in a number of ways. We prefer an oblique type of anastomosis, placing fine atraumatic sutures through the serosa and muscularis. The anastomosis should be done over a splinting catheter, which is left in place for at least 21 days. A nephrostomy should be done at the time of anastomosis, both tubes being brought out through the same kidney incision.

Injuries of the lower portion of the ureter can sometimes be treated by a ureteroneocystostomy. It is preferable to anastomose the ureter as close to the posterior wall of the bladder as possible. An anastomosis into the dome of the bladder should be done only if the length of the ureter is such that it can be brought down no farther. A splinting catheter should be used in these cases also. This can be brought out through the urethra. A Foley catheter inserted through the urethra alongside the splinting catheter is a great help in stabilizing the latter.

Four cases of ureteral injuries were seen; one of these was treated at another hospital. Another patient was seen in consultation at a Korean hospital seven months after the original injury. It will be mentioned in passing and not included in the case presentations

Our first introduction to ureteral injury was a Korean soldier who had been wounded 7 months prior to the time he was seen. A urinary fistula had developed in the left flank. Excretory urogram revealed the fistulous tract to arise from the ureter about 6 cm. below the ureteropelvic junction The patient had sustained wounds of the small intestine and ureter. The former had been repaired but the latter remained untreated. Subsequently a retroperitoneal abscess developed and was drained; otherwise, the patient received no treatment for the ureteral injury. When asked to see the patient in a Korean hospital, he was beyond the stage in which a ureteral repair could be accomplished. A left nephrectomy was done thereby curing his fistula.

Case 11: A 32 year old Korean was hit by shrapnel sustained wounds of the abdomen and extremities. He was initially explored at a Marine Medical Company where 15 inches of small intestine were removed, and an end-to-end anastomosis was carried out His other wounds were debrided and dressed. Twenty-four hours postoperative, his abdomen became distended. A Levine tube was inserted which relieved the distention considerably. The patient was sent to this hospital 13 days postoperative. His abdomen was distended with fluid. A paracentesis yielded 6050 cc of straw colored fluid He complained bitterly of left flank pain. His left flank was distended and dull to percussion. A tap of that area yielded straw colored fluid with a specific gravity of 1.013. Cystoscopy was then performed and a retrograde pyelogram made (fig. 2). On examining the bladder, no urine was seen coming from the left ureteral orifice. Clear urine was spurting from the right. A 5F ureteral catheter was passed 26 cm on the right with ease. On the left, obstruction was met at 15 cm. Urography revealed a perforation of the ureter at that point with extravasation of dye into the adjacent area Some dye reached the left kidney which revealed moderate dilatation of the pelvis and calyces.

The patient was taken to surgery and operated on through a left lumbar incision The ureter was exposed and the tear isolated. As the ureter was not completely severed, a T tube was inserted and the retroperitoneal space drained. The missile which caused the damage was removed from the body of the vertebra adjacent to the damaged portion of the ureter.

The postoperative course was uneventful and the patient did well and was up and about in 3 days Ten days later, the T tube was removed However, the ureterocutaneous fistula thus formed did not heal. The patient was again explored 2 weeks later through a left lumbar incision and the fistula was isolated There was much scar tissue present at the former site of injury. Freeing the ureter and removal of the scar tissue required complete severance of the ureter. An oblique anastomosis around a splinting tube was carried out This tube was brought out with a nephrostomy tube The patient did well postoperatively. He was evacuated to a Korean hospital 20 days later The followup is not available.

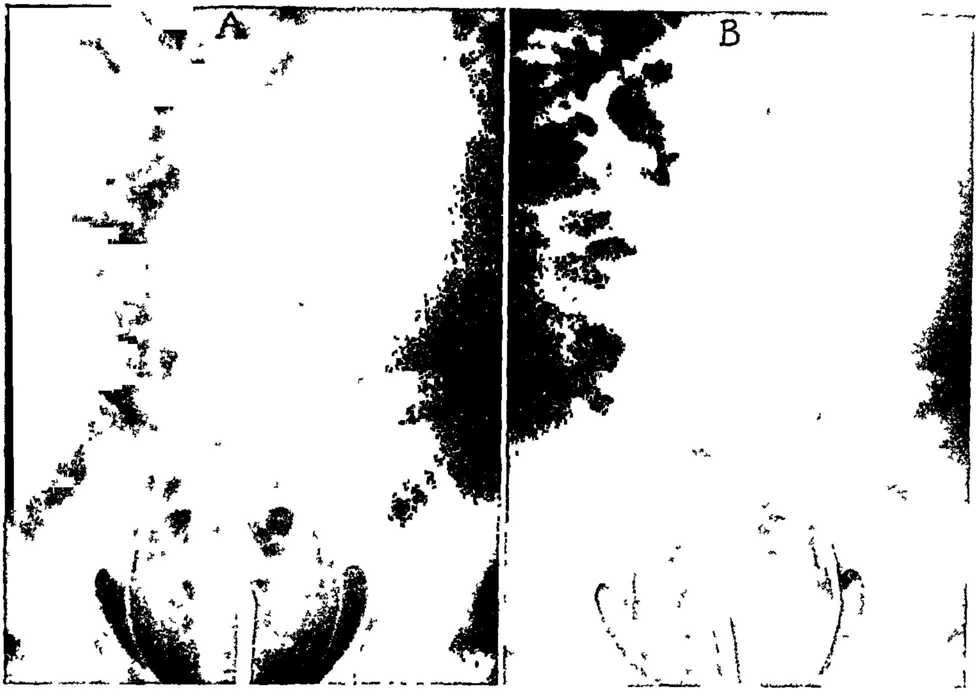

FIG. 2. *A*, left ureteral catheter passed to point of injury. Shrapnel seen at site of injury. *B*, retrograde ureteropyelogram reveals laceration of ureter with pooling of dye lateral to it.

It is quite possible that proper healing of the ureter would have taken place had the T tube been left in place for at least 21 days.

Case 12: A 19 year old private first class, USMC, hit by fragments from an exploding land mine, sustained multiple wounds of the lower extremities, along with a compound comminuted fracture of the left tibia. The patient had no findings suggestive of abdominal or chest injury at this time. He was taken to the operating room where debridement of his wounds was carried out. A Steiman-pin was inserted into the left tibia in preparation for an intramedullary nailing which was carried out 12 days later.

Twenty-seven days after the initial injury, the patient experienced a severe right lower quadrant abdominal pain which radiated into the right testicle and right costovertebral angle. The patient was in agony. Examination revealed muscle guarding of the right side of the abdomen with marked tenderness in the right costovertebral angle and flank. Urinalysis was normal. It was suspected that patient was having right ureteral colic. An excretory urogram revealed a nonfunctioning right kidney and a normal left kidney. A metallic foreign body was lying just lateral to the course of the lower ⅓ of the right ureter. Cystoscopy was performed. The right ureteral orifice was edematous and the intramural portion of the right ureter was dilated. The tip of the ureteral catheter could not be inserted into the orifice of the right ureter. No opaque shadows were seen along the course of the right ureter.

As the right lower quadrant of the abdomen became increasingly tender and the patient had no relief from his pain, it was decided to do an exploratory laporotomy. He was explored through a right rectus incision. The peritoneal cavity was negative so the peritoneum was closed. An extraperitoneal exploration was then carried out by reflecting the peritoneum medially. The right ureter was dilated and tense in its lower portion. Dissection down to ureterovesical junction was carried out. There was no stone palpable in the lower ureter. The ureter was then opened and a ureteral catheter inserted. An attempt to pass a catheter into the bladder was unsuccessful as an obstruction was present in the intramural portion of the ureter. The bladder was then opened to facilitate further exploration. The intramural portion of the ureter was found to be scarred and strictured. This was most likely caused by the aforementioned missile traversing this portion of the ureter. A ureteroneocystostomy was carried out by means of the "fish-mouth" technique and the bladder was closed primarily. Drains were left extraperitoneally along the paravesical space.

The patient did well after operation. His pain was relieved and healing was progressing favorably when he was transferred to a Naval hospital in Japan.

Comment: The few cases of ureteral injuries seen serve to emphasize the fact that these cases are difficult to recognize initially. If the path of the missile had been traced in case 10, the diagnosis could have been made and the injury treated initially. This is to the patient's advantage, as the second procedure is always rendered difficult by adhesions, infection, urine in the tissue spaces, and the weakened condition of the patient. A preoperative excretory urogram in cases suspected of ureteral injury is sometimes all that is necessary, although the recommended procedure is cystoscopy and retrograde urography. It is well to re-emphasize that the injury of the ureter has to be *suspected* if it is to be diagnosed initially. The condition of the patient and the facilities available will determine what should be done to confirm one's suspicions of ureteral injury.

SUMMARY

A symposium of war injuries of the upper urinary tract and illustrative cases have been presented. The incidence of abdominal and chest injuries have been reduced, as compared with World War II, as a result of the use of the so called "armor-vest." The incidence of postoperative infection with resultant complications, as compared with World War II, has been reduced by the liberal use of antibiotics after injury and operation. These advances, along with the excellent treatment given the wounded in the forward aid stations, have salvaged many lives from the field of battle.

ACKNOWLEDGMENTS

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THE PROBLEM OF PRIMARY MEGALO-URETER

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In recent years congenital anomalies of the urinary tract in children are being recognized and reported in the literature in increasing numbers. This has resulted to a great extent from the wider recognition of the principle that a persistent urinary tract infection calls for detailed examination.

Among these abnormalities dilatation of the ureter, unilateral or bilateral, is no longer a rarity. Campbell[1] has classified such dilatations into two groups, primary and secondary. A diagnosis of primary megalo-ureter should be confined to those cases in which no mechanical obstruction can be found to account for the ureteral dilatation. The term megalo-ureter was first used by Caulk[2] in 1923 to describe such a deformity in a case in which no obstructive lesion was demonstrated and in which the ureteral orifices appeared normal on cystoscopic examination. Prior to this, similar ureteral dilatation without apparent cause had been noted by other observers (Saintu[3] 1896, Fortescue-Brickdale[4] 1905, and others).

The purpose of this paper is to review the results of some methods of treatment used for this condition in the past, and to consider briefly whether the operative procedures have yielded significant clinical benefits. It would be tempting also to discuss the etiology of megalo-ureter, but with the evidence available in the cases presented here, any conclusion reached would be largely speculative.

Before making a diagnosis of primary megalo-ureter it is well to remember its rarity. Such a diagnosis was made in only 4 patients admitted to University Hospital since 1935: two further cases have been excluded from the present study owing to inadequate record of bladder function. Similarly, Campbell[5] could only find two cases of primary megalo-ureter among several hundred cases of dilatation of the ureter. To establish the diagnosis two criteria must be fulfilled:

1. DILATATION OF THE URETER

Ureteral dilatation may be demonstrated by excretory or retrograde pyelography, or by cystogram if reflux of urine from bladder to affected ureter is present. The value of a delayed or voiding cystogram is emphasized, for in some cases no sign of reflux is found in early films but is only observed in those made after an interval of one-half hour or an hour (Stewart[6]).

Presented to the New York Section of the American Urological Association, April 22, 1953.

[1] Campbell, M.: Clinical Pediatric Urology. Philadelphia: W. B. Saunders Co., 1951.

[2] Caulk, J. R.: The importance of the ureterovesical valve. J. Urol., 9: 315, 1923.

[3] Saintu, O.: Note sur un cas de rétention d'urine chez le foetus avec perméabilités du canal de l'urèthre, J. de Méd. de Paris, 8: 332, 1896.

[4] Fortescue-Brickdale, J. M.: A note on congenital dilatation of the ureters. Bristol Med. Chir. J., 23: 231, 1905.

[5] Campbell, M.: Primary megalo-ureter, J. Urol.., 68: 584, 1952.

[6] Stewart, C. M.: Delayed cystograms. J. Urol., 70: 588, 1953.

The diameter of the ureter is increased; this may be unilateral or bilateral. In the present study it has been noted that the circumferential dilatation is not accompanied by commensurate increase in length, and kinking of the ureter is not a marked feature of these cases. A similar observation has been made by others (Campbell,[5] Hepler[7], Wayman[8]), and Hinman[9] has considered multiple angulation to be indicative of an obstructive etiology. The renal pelvis and calyces of these patients do not show the degree of dilatation which might be expected in the presence of such ureteral deformity

2. ABSENCE OF OBSTRUCTION

Obstruction in the course of the lower urinary tract must be excluded. The more gross types of obstructive lesion at the lower end of the ureter or at the bladder neck should present no difficulty in demonstration. But exclusion of obstruction at the bladder level cannot be regarded as certain without careful assessment of vesical function by cystometric examination and estimation of residual urine. Bladder dysfunction due to neurogenic disturbances may be reflected in the ureter, and many reported cases of so-called primary megalo-ureter would properly be excluded from this group if such full investigation had been carried out.

It is an accepted fact that long standing ureteral infection can produce some degree of dilatation of the ureter. With this knowledge it would be desirable, before establishing a diagnosis of primary megalo-ureter, to exclude infection as a possible etiological factor. In the present series of cases, however, infection is an invariable accompaniment of the stasis associated with ureteral dilatation. For this reason it is felt that cases with infection should not be excluded from this category if the criteria mentioned above are fulfilled.

Some observers on this subject have stated that additional criteria are necessary to confirm the diagnosis of primary megalo-ureter. Campbell considers that vesico-ureteral reflux with a relaxed immobile ureteral orifice is a characteristic finding in this condition Although reflux may be present, it appears not to be invariably the case; reflux occurred in only one of the 4 patients presented here (case 1) Indeed its absence tends to confirm a diagnosis of primary ureteral dilatation provided that an obstructive lesion of the lower ureter has been excluded Also, on cystoscopy we are impressed with the normal appearance of the ureteral opening in these cases and have observed patulous orifices in only one case

CASE REPORTS

Case 1 An 11 year old girl, S P, was first seen in August 1950 Her mother gave a history that the child was well until two years old when she had a convulsion accompanied by temperature of 102F. During the course of illness, which lasted a few days, her doctor found that she had a urinary tract infection which responded promptly to treatment with a sulfonamide preparation. This was the first attack of many similar episodes which occurred at intervals of three to five months and all were accompanied by the presence of pus cells and organisms in the urine. Since the age of eight it had become increasingly difficult to control the infections and attacks had become prolonged. Her mother stated that she appeared to have no difficulty in passing urine at any time.

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[7] Hepler, A B Non obstructive dilatations of upper urinary tract in children J A M. A 109: 1602, 1937

[8] Wayman, T B Surgical treatment of megalo-ureter J Urol , 61: 883, 1949

[9] Hinman, F Obstructive hydroureteral angularity with hydronephrosis in children Arch Surg , 18: 21, 1929

The patient was a healthy looking girl of normal size and weight and no gross abnormality was found on physical examination. She voided urine with good force although 55 cc residual urine was present following micturition and this showed 10 to 15 white blood cells and rod shaped organisms when examined microscopically. Renal function tests were within normal limits. A cystometrograph was performed at this time and although there was large bladder capacity (400 cc) the shape of the curve was normal. Panendoscopy and cystoscopy (August 16, 1950) revealed a normal bladder with no trabeculation and no vesical neck obstruction. Both ureteral orifices were patulous and were easily catheterized; on retrograde injection of dye moderate increase in ureteral diameter was noted. A cystogram revealed the presence of bilateral ureteral reflux.

At operation on August 18, 1950, the left ureter was exposed throughout its length by a left pararectal incision. It was found to be dilated to three times its normal size but showed active peristalsis on stimulation. The dilatation continued to the point where the ureter entered the bladder. The caliber of the ureter was reduced throughout its length by removal of a strip comprising approximately two thirds of its circumference as described by Crabtree and also used by Wayman. The lower end of the ureter was then re-implanted into the bladder by a fish-mouth technique. The operation was completed by suprapubic cystotomy.

The patient made a good recovery from operation and in view of the ureteral reflux her cystotomy drainage was maintained to insure continuous and complete bladder drainage. However, repeated episodes of urinary tract infection occurred which could be controlled by various antibiotic agents. A cystogram made on October 31, 1950, showed that ureteral reflux persisted bilaterally. Three months after operation, following a trial of voiding with the suprapubic tube clamped, only a few cubic centimeters of residual urine remained in the bladder and her suprapubic drainage tube was removed. The removal of the suprapubic tube appeared to lessen the frequency of attacks of urinary infection, and a cystogram made one year later demonstrated diminution in reflux on the right side but it was still present on the left. Since this time she has continued to make very satisfactory progress with only one attack of urinary infection during the the past year and recent excretory urograms give evidence of good renal function with no hydronephrosis.

Commentary on case 1: This was the only case of the series in which ureteral reflux was demonstreated preoperatively. It is significant that she was found to carry residual urine of 50–100 cc although she was observed to void with an uninterrupted and forceful stream with apparent complete emptying of the bladder. In view of the normal vesical function it was assumed that this amount of residual urine did in fact represent the volume of reflux. Crabtree[10] has reported a similar case in which incompetence of the ureteral valves allowed reflux of urine during voiding.

In this case a period of 3 months' vesical drainage by cystotomy did not diminish reflux nor did it improve the degree of megalo-ureter on either side. It is noteworthy that following removal of the suprapubic drainage tube her pyrexia subsided and urinary infection markedly improved. A cystogram made 13 months after operation revealed only minimal reflux into the lower third of the ureter on the right but was still present on the opposite side which had been treated surgically. Although the left ureter was poorly visualized in this cystogram the x-ray suggested that the left ureter was in fact as dilated as before operation. The last excretory urogram made in August 1952 (two years after operation) shows good renal function on both sides with no evidence of hydronephrosis or calyceal dilatation. This fact coupled with the satisfactory clinical progress that the child is making is strong evidence that little benefit was derived from operation. It would be interesting to know the degree of ureteral reflux which may now be present, but the mother is reluctant to bring her child to the hospital for this purpose as she is making such excellent progress.

Case 2. J. O., a girl, was brought to University Hospital in July 1950, when 4 years old. She had been well until the age of 18 months when her mother noticed that she had pain on urination. At this time her doctor found pus cells in the urine. Since this first attack she had had four episodes of pyrexia accompanied by frequency of micturition every one to two hours and an infected urine. At no time was there a history of flank pain or tenderness on palpation in the renal areas. Physical examination was negative and tests showed satisfactory renal function (blood urea nitrogen 16 mg. per cent; phenolsulfonphthalein excretion 48 per cent in 2 hours). An excretory urogram revealed a severe degree of bilateral ureteral dilatation with minimal hydronephrosis on the left. No evidence of ureteral reflux was demonstrated in a cystogram.

At operation on July 28, 1950 the right ureter was found to be approximately 2 cm. in diameter but showed good peristalsis. The dilatation extended from the kidney to a point approximately one inch from the bladder. At this point the ureter was of normal size and through this narrowed portion a No. 6 ureteral catheter was passed with ease into the bladder. It was therefore felt that obstruction at the lower end of the ureter could be confidently excluded. The ureter was detached from the bladder at the ureterovesical junction and this narrower portion excised. Approximately one-third of the diameter of the ureter was resected throughout its length and re-implanted into the bladder by an elliptical anastomosis at a point above and to the right of the previous ureteral opening. The ureter was drained by ureterostomy and a cystotomy tube was left in situ suprapubically. A cystogram made 3 months after this operation now showed reflux on the operated side.

On October 9, 1950, at a second operation, exposure of the left ureter showed

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[10] Crabtree, E. G.: Plastic operation for the relief of megalo-ureter. Trans. Amer. Assoc. G. U Surg., 30: 311, 1937.

similar findings to those on the right side. Again no evidence of obstruction could be demonstrated at the lower end of the ureter and approximately 4 inches of the lower ureter were resected and the free end re-implanted into the bladder by elliptical anastomosis. On this side no longitudinal segmental resection was performed. A cystogram made one month following this procedure now revealed that reflux was present bilaterally.

The child made satisfactory progress following these operations and 2 months after the second operation the cystotomy tube was removed and the suprapubic fistula allowed to close. At this point severe episodes of pyrexia occurred and could only be controlled by sustained catheter drainage. From then until the present time removal of the indwelling catheter has invariably been accompanied by a recurrence of these attacks of pyrexia and flank pain. A recent excretory urogram (fig. 1, *A*) showed satisfactory function although ureteral dilatation persists and on cystogram (fig. 1, *B*) it is seen that she has a severe degree of megalo-ureter and hydronephrosis. At no time during the course of this patient's illness and treatment have renal function tests revealed any gross deviation from normal.

Commentary on case 2: In this case, although the dilatation of right ureter appeared to be initially improved by operation, the final result and persistence of megalo-ureter show that surgery did little to benefit the child. In fact, ureteral reflux which was not present in the original x-rays appeared in cystograms made after operation. It is significant that continuous bladder drainage produced no improvement in her ureteral dilatation.

In spite, however, of these abnormalities and a urinary infection from which she is seldom free, the child remains surprisingly active and healthy; this fact is reflected in the comparatively normal renal function tests.

This case also illustrates the value of a cystogram in demonstrating the true degree of ureteral dilatation. The excretory pyelogram (fig. 1, *A*) does not suggest the gross megalo-ureters which in fact exist, but which are dramatically revealed in a cystogram made shortly afterwards (fig. 1, *B*).

Case 3. A 4 year old girl, L. A., was admitted to hospital in March 1952. For

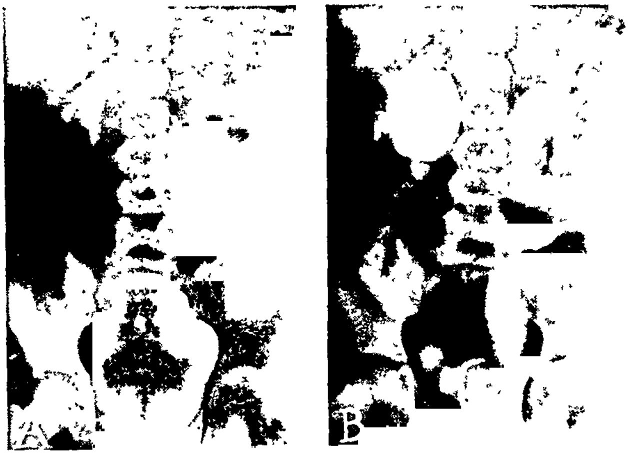

FIG. 1. Case 2. *A*, excretory urogram and *B*, cystogram 2 years after operation showing recurrence of dilatation of right ureter. Cystogram reveals true degree of ureteral dilatation which is not demonstrated in excretory urogram made 2 days previously.

two and a half years she had suffered from recent episodes of high fever, frequency and pain on micturition. During each of these attacks her urine was found to contain pus cells and bacteria, and although initially the infection responded rapidly to treatment with sulfa drugs it had recently become refractory to therapy. At no time had there been any difficulty in initiating micturition.

On admission, physical examination was negative and she was seen to void with a good stream. A catheter specimen of urine examined microscopically showed 5 pus cells per high power field, and numerous bacilli which proved on culture to be E. coli. The blood urea nitrogen was 17.5 mg. per cent, the plasma CO_2 combining power 38 vols. per cent, and serum chlorides were 103 m/Eq. per liter.

Excretory urograms revealed dilatation of both ureters, with some degree of hydronephrosis on the left. The calyces, however, were sharply outlined with no loss of "cupping." A cystogram showed no evidence of reflux. A normal cystometrograph and absence of residual urine after voiding suggested good bladder function. On cystoscopy and panendoscopy the bladder appeared normal, with an adequate vesical neck outlet. No ureterocele or other obstruction was seen at either ureteral orifice, through which No. 5 catheters could be passed with ease.

At operation on March 31, 1952, the lower third of the left ureter was exposed extraperitoneally by a transverse lower abdominal incision. The ureter was approximately 2 cm. in diameter throughout its course until, at a point 3 cm. from the bladder, the dilatation ceased and the remaining portion of the ureter appeared to be of normal size. Active peristalsis was noted in the dilated portion of the ureter. The ureter was divided at its junction with the bladder and the narrowed section removed, together with 3–4 cm. of the dilated portion. The remaining ureter was re-implanted into the bladder at a point higher on the lateral wall, by elliptical anastomosis. A pathological report of the removed portion read as follows: "Dilatation of the ureter with hypertrophy of muscularis and heavy focal collections of lymphocytes in the muscularis."

The patient made a good recovery from operation, but convalescence was complicated by attacks of high temperature and pain and tenderness in the left costovertebral angle. Vigorous therapy with antibiotic drugs during the next 3 months was required to control these episodes of infection but her flank pain became progressively more severe.

A cystogram made at this time revealed reflux of urine on the side of operation, and it was believed that these symptoms were due to an ascending pyelonephritis. During July 1952 she had persistent pyrexia, her general condition deteriorated and the child became pale and listless. Although studies showed good renal function, urgent treatment was considered necessary to prevent severe renal damage and possible nephrectomy.

Accordingly, at a second operation on August 11, 1952, the left ureter was excised in its entirety, and replaced by an isolated segment of ileum as reported by McLean and Fais[11] following its experimental use in dogs. In view of the recognized association of megacolon and ureteral dilatation this procedure was

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[11] McLean, D. W. and Fais, O. G.: The use of segments of small intestine as ureters. J. Urol., 68: 190, 1952.

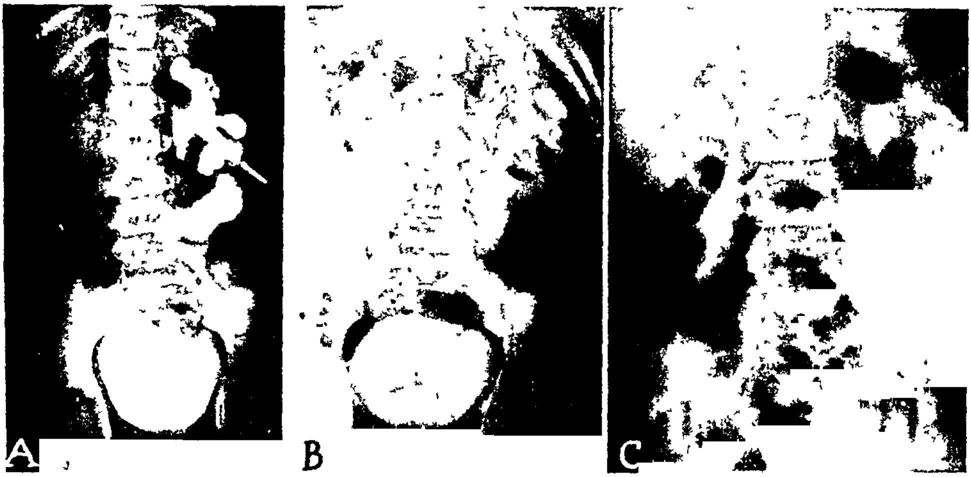

Fig. 2. Case 3. *A*, injection of radio-opaque dye through nephrostomy tube 3 weeks after replacement of left ureter by isolated loop of ileum. *B*, cystogram demonstrating reflux up ileal loop. *C*, excretory urogram 4 months following use of ileal loop to replace left ureter.

undertaken after x-ray investigation had excluded any intestinal abnormality. At a point about 18 inches from the ileocaecal valve a loop of ileum and mesentery was isolated. This loop was swung across in front of the colon and anastomosed to the renal pelvis and bladder, after the removal of the affected ureter. Active peristalsis was again observed during the manipulation of the ureter. The operation was completed by the insertion of a nephrostomy drainage tube.

Following this surgery the patient's general condition improved steadily and although her urine remained infected she became asymptomatic and the pain and tenderness in the left costovertebral angle subsided. During the first few weeks the urine contained varying amounts of mucus from the transplanted intestine but this gradually subsided and is now completely absent.

Two weeks after operation radio-opaque dye injected through the nephrostomy tube and observed during fluoroscopic screening was seen to pass rapidly from renal pelvis to bladder (fig. 2, *A*). A cystogram also made at this time showed that reflux occurred up the intestinal loop (fig. 2, *B*). However, as drainage from the renal pelvis was so efficient the nephrostomy tube was removed 21 days after operation and the wound healed rapidly.

The initial satisfactory progress that this child made has been maintained and when last seen 4 months after operation her urine contained only a few pus cells with an occasional bacillus when examined microscopically.

Commentary on case 3: Several writers on this subject (MacMyn[12], Hurst and Gaymer-Jones[13], Swenson and associates[14] and Lewis and Kimbrough[15]) have drawn comparisons between primary megalo-ureter and congenital megacolon,

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[12] MacMyn, D J On dilatation of the ureters and hydronephrosis in childhood. Brit. J. Urol., **1:** 150, 1929

[13] Hurst, A F and Gaymer-Jones, J : A case of megalo-ureter due to achalasia of the ureterovesical sphincter. Brit. J. Urol., **3:** 43, 1931.

[14] Swenson, O , MacMahon, H. E., Jaques, W E. and Campbell, J. S. A new concept of the etiology of megaloureters New Eng J. Med., **246:** 41, 1952

[15] Lewis, E. L. and Kimbrough, J. C.: Megalo-ureter New concept in treatment. South. Med. J., **45:** 171, 1952

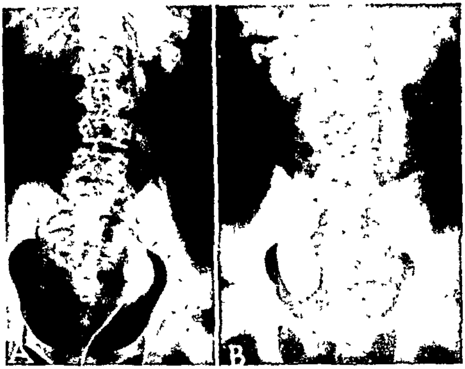

FIG. 3. Case 4. Retrograde pyelograms (1931) showing bilateral megalo-ureter.

and indeed the two conditions are sometimes co-existent (Moore and Lawrence[16]). In this case and in case 2 it was noted at operation that the dilated portion of ureter had inherent contractibility when stimulated and terminated from 2 to 4 cm. from the ureterovesical junction, these lower few centimeters of ureter being of normal size. Such an appearance certainly seems to suggest an analogy to the dilated and hypertrophic colon proximal to a narrow section of bowel which Swenson and others[17, 18] have shown to be devoid of parasympathetic nerve supply in congenital megacolon. Kimbrough[15] reports encouragingly on the results of resection of this normal appearing segment of ureter and vesical re-implantation of the dilated ureter. It has been our experience, however, that such an operation produced no improvement in the degree of megalo-ureter in the two cases in which it was employed.

In this case excision of the narrower portion of ureter and re-implantation into the bladder allowed ureteral reflux of urine which had not been present prior to operation. This appeared to initiate a series of severe episodes of ascending infection and pyelonephritis. It is possible that such reflux might be prevented by allowing a short segment of ureter to lie free in the bladder as practiced by Kimbrough who considers that such a procedure is helpful in preventing this complication.

The use of an isolated loop of intestine to replace the ureter undoubtedly improved the child's condition symptomatically and the recurrent episodes of pyelonephritis ceased. Up to the present time the result of this operation appears very satisfactory, but a longer period of observation will be necessary before final evaluation of such a procedure can be made. It may be pertinent to remark on the possibilities of such an operation in the treatment of other conditions in which replacement of a ureter is necessary.

[16] Moore, T. C. and Lawrence, E. A.: Congenital malformation of the rectum and anus. Surg. Gynec. & Obst., 95: 281, 1952.

[17] Swanson, O., [illegible] L.: Hirschsprung's disease: New concept of etiology. Ne[illegible]

[18] Bodian, M. an[illegible] disease: A new concept. Proc. Roy. Soc. Med., 42: 225, 1[illegible].

Case 4. M. E., an unmarried 33 year old woman, has been observed at University Hospital since she was nine, when her mother stated that she had had episodes of fever accompanied by flank pain since the age of two. Cystoscopy revealed an inflamed but otherwise normal appearing right ureteral orifice and a normal left ureteral orifice. Catheterization of both ureters was easily performed and there was no evidence of obstruction. The specimens of urine obtained from the ureters were heavily loaded with pus cells and bacilli. Pyelo-ureterograms (fig. 3, *A* and *B*) made at this time revealed bilateral ureteral dilatation but the renal calyceal systems did not show a commensurate degree of deformity although hydronephrosis was present.

At intervals for the next 6 years lavage of both ureters was carried out and with this treatment she remained in good health and remarkably free from symptoms, and the intervals during which the bladder urine was free from infection became increasingly longer.

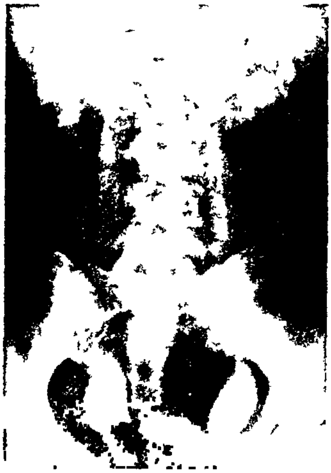

FIG. 4. Case 4. Retrograde pyelograms (1948). In spite of persistence of bilateral megalo-ureter, patient's renal function remains good, she has uninfected urine and is leading an active life No operation was performed

In 1935, however, when the patient was aged 15, severe urinary tract infection recurred accompanied by bilateral flank pain radiating to the lower abdomen. It was noted that these bouts of infection coincided with her menstrual periods. Owing to the increasing severity of the attacks and their persistent association with menstruation, an x-ray sterilization was considered advisable. This produced a dramatic amelioration of her urinary symptoms. The improvement was maintained and she was well until 1948 when menstruation re-commenced and pain recurred, to be relieved once again when x-ray therapy terminated her periods.

Since this time she has remained entirely free from symptoms and has led an active and healthy life as a teacher. It is noteworthy that her urinary tract infection was promptly cleared on the institution of treatment with sulfonamide drugs, and has not returned. Her ureterograms made at intervals since 1929 show that the degree of ureteral dilatation has not materially changed, nor has there been evidence of increasing hydronephrosis (fig. 4). Recent renal function tests show that the phenolsulfonphthalein clearance was 58 per cent in 2 hours.

Commentary on case 1. The satisfactory result in this case from conservative management adds weight to the doubts cast on the value of any surgical interference in these cases It must be noted again, however, that the dilatation of her ureters has persisted unchanged throughout the course of our observation

A further point of interest in this case is the manner in which the infection of the urine seemed to be closely associated with menstruation and was cleared by an artificial menopause Such an association may favor the possibility of an hormonal factor in the etiology of this condition In this respect also the anatomical relationship of the uterine artery to the lower end of the ureter must not be forgotten

DISCUSSION

At the present time the many theories of the cause of primary megalo ureter are all largely conjectural. With so little understood about the etiology it is not surprising that varied surgical approaches to the problem have been attempted

It had been believed in the past that suprapubic cystostomy alone had, in some instances, resulted in decrease in the size of the ureters In the light of present knowledge, however, it is probable that those cases in which improvement has been noted, were, in fact, not true primary megalo-ureters, but cases in which faulty vesical function was present Neither suprapubic cystostomy nor continuous bladder drainage by catheter has resulted in diminution of ureteral dilatation in any of the cases reported here

Our present investigation has sought an answer to the question of whether the operative procedures in these cases have yielded significant clinical benefits

Operation in all 3 cases was performed in an effort to alleviate the following conditions. gross bilateral ureteral dilatation, infection in the urine, and episodes of sepsis All three of the cases following operation have shown persistence of the ureteral dilatation, and have continued to have infection of the urine Based on the stated criteria one is forced to conclude that results hoped for have not been attained

Compared to these 3 cases the other patient in whom no operation was performed also has dilated ureters, but she is clinically well and has been free from infection for nearly ten years It appears that she has fared better than the others

Our present opinion regarding the management of such cases would be this: the clinician who faces any problem of this sort must focus his attention on excluding evidence of obstructive uropathy which might be amenable to surgical correction It is only when all such factors are found to be lacking that a diagnosis of primary megalo ureter can be established It seems that renal function remains surprisingly good in these cases, and that the prognosis need not be as pessimistic as the degree of ureteral dilatation would at first suggest

Perhaps in this particular type of case it might be better to focus our therapeutic efforts along conservative antibacterial avenues and be less concerned with correction of ureteral dilatation

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THE INTRAPSOAS TRANSPLANT OF MEGALO-URETER

HJALMAR E. CARLSON

In congenital megalo-ureter the etiology is as yet unknown but has been described as due to 1) neurogenic causes, 2) obstructive causes, or 3) due to developmental arrest. Whatever the basic cause may be there is some type of neuromuscular dysfunction involved. When the ureters are involved in neuromuscular dysfunction usually both ureters are affected, and usually equally, although I have seen a number of cases where only one ureter was involved. Of the 12 cases I have seen, few have had any actual obstruction at the ureterovesical orifice and catheters can readily be passed. Some cases may have vesical neck contracture or strictures but in most cases there is no such obstruction.

In the treatment of megalo-ureter ureteral meatotomies prehaps have been of some value even though there is no actual stricture. Transurethral resection of the vesical neck to facilitate drainage with or without contracture of the bladder neck has been reported favorably. Re-implantation of the ureter into the bladder to create a large ostium either with or without the pull-through technique has been reported to be of value. I have seen some very good results with this method. The excision of the redundant ureter, with end-to-end anastomosis and preservation of the ureterovesical orifice has its advocates. Permanent ureterostomies and permanent nephrostomies have been performed. Even with this approach the disease is usually although not always progressive, and death is the end-result from pyelonephritis, uremia, hypertension and coronary disease. In an attempt to stimulate the emptying of the megalo-ureter I reasoned that perhaps the voluntary muscles, if they could be brought into play, might be of some value. In some way perhaps then the dysfunction could be overcome or at least arrested. The psoas muscle lying along the spine and just beneath the ureter seemed the most logical muscle to use, inasmuch as it is accessible from a point above the kidney as well as down into the pelvis. The number of cases of megalo-ureter seen by the average urologist is not great, and suitable cases are not always forthcoming, so I am therefore only able to report on 2 cases in which the ureter has been implanted within the psoas muscle; however, I would like to present the technique to you since only by observations of several can the procedure be truly evaluated.

The technique of the operation is simple (figs. 1 and 2). The patient is placed on his side with the table broken in typical kidney position. The incision is extended well into the lower quadrant. Since the patients are children the bladder lies relatively high and the juxtamural ureter is therefore not difficult to visualize. The dilated ureter with its various tortuosities and adhesions is freed from the kidney to the bladder. With the additional length gained from freeing of the adhesions it can then be readily transplanted into a trough in the psoas muscle. This trough should extend from a point just below the renal pelvis to a point just proximal to the bladder, and is made as deep as possible. The psoas muscle

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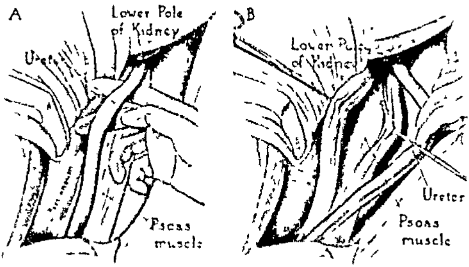

FIG. 1. *A*, ureter is freed from kidney to bladder. *B*, trough in psoas muscle is prepared.

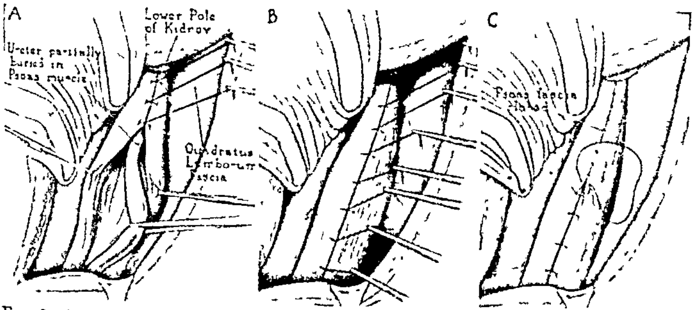
A
Lower Pole of Kidney
Ureter partially buried in Psoas muscle
Quadratus Lumborum fascia
B
C
Psoas fascia closed

FIG. 2. *A*, ureter is buried within psoas muscle with interrupted sutures of chromic catgut. *B*, almost entire ureter can be buried. *C*, psoas fascia is closed and fascial nephropexy then done.

is approximated over the ureter with interrupted chromic catgut sutures and the psoas fascia with a running catgut suture. The perirenal fascia is used to suspend the kidney to prevent angulation of the ureteropelvic junction.

CASE REPORTS

Case 1. M. 39148, E. S., a girl, aged 1 year, was first seen in January 1949 because of urinary incontinence and apparent pain on urination. There was a history of a common anal and vaginal opening at birth and this had been previously corrected on the gynecology service. On cystoscopic examination, January 28, 1949, bilateral hydro-ureters were found. Sulfonamides and antibiotics relieved her symptoms. Blood chemistry studies were normal. Approximately one year later, on December 9, 1949, recheck retrograde pyelograms (fig. 3) showed some increased dilation of the ureters, and there was still further increase on pyelograms on October 27, 1950 (fig. 3). On December 1, 1950, the right ureter was freed from the kidney to the pelvic brim and loosely placed in the psoas trough prepared for it. The ureter was found to be approximately 1 cm. in diameter and, as is usually true, it is always larger and more tortuous at operation than on the x-ray. Five interrupted chromic No. 1 catgut sutures were loosely

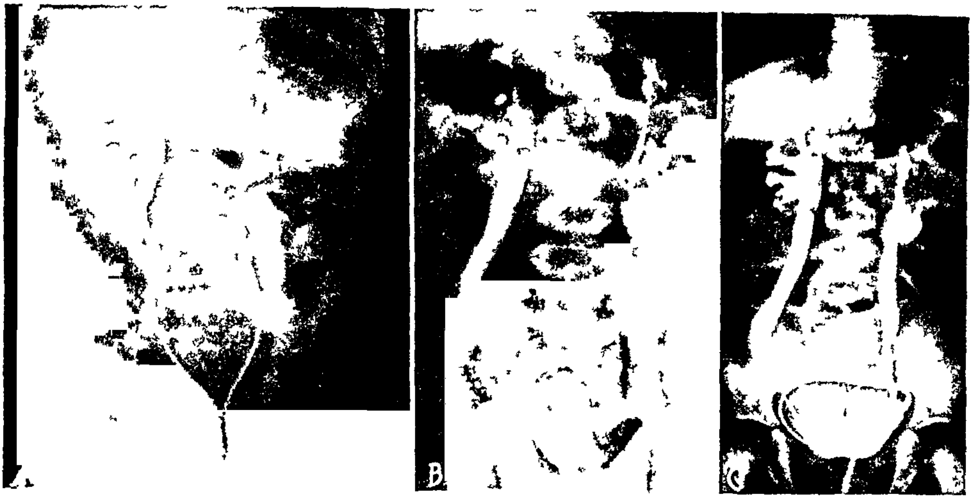

Fig. 3. Case 1. *A*, preoperative pyelogram 2 years before operation. *B*, preoperative pyelogram 1 year before operation. *C*, preoperative pyelogram.

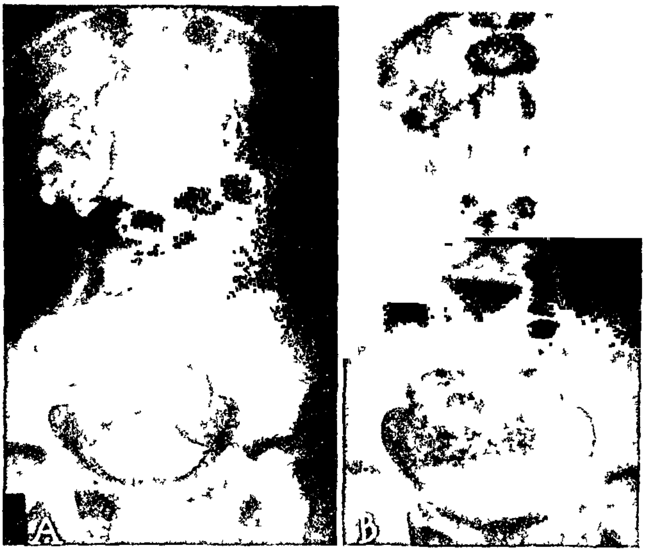

Fig. 4. Case 1. *A*, pyelogram 2 months after transplantation of right megalo-ureter into psoas muscle. *B*, excretory urogram 2½ years after operation.

approximated over the ureter, and the psoas fascia closed with a running suture of plain catgut. On January 5, 1951, a retrograde pyelogram was made and diminution in the size of the right ureter was observed. Excretory urograms were unsatisfactory because of poor renal function. On March 17, 1953, an excretory urogram disclosed some increased dilation of the right ureter (fig. 4). Urine examination was negative for albumin and microscopically there were 5 to 8 pus cells per high power field. The blood chemistry showed nonprotein nitrogen 25 per cent, CO_2 42 volume per cent, and chlorides 552 mg. It was my feeling that had the ureter been buried in a more satisfactory manner a more permanent result would have been obtained.

Case 2. M. 42661, B. H., a girl, aged 9 years, was seen because of enuresis.

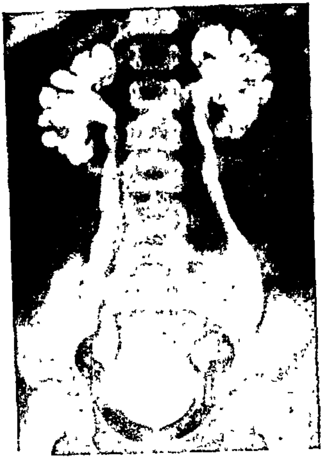

FIG. 5. Case 2. Preoperative pyelogram

Urine examination showed 10–15 white blood cells per cubic millimeter but it was otherwise negative. An excretory urogram taken August 13, 1952 showed no renal function. Retrograde pyelograms were taken August 14, 1952, and bilateral hydro-ureters of equal extent were demonstrated (fig. 5). On August 29, 1952, an intrapsoas transplant of the left ureter was performed. On this occasion the psoas trough was both deeper and more extensive than in the previous case and extended from the kidney to within one or two centimeters of the bladder. Suturing was also more complete and the psoas muscle was tightly rather than loosely closed over the ureter. As previously, the ureter was greatly dilated and approximated 2 cm. in diameter. The psoas fascia was closed after approximating the muscle with No. 1 interrupted chromic catgut sutures. The nonprotein nitrogen, which had been 51 prior to operation, rose after operation to 83, but 2 weeks postoperatively, on September 13, 1952, it was 56 mg. per 100 cc. Blood chemistry studies made subsequently have shown some variations but on the last study, March 20, 1953, the nonprotein nitrogen was 45. Part of this variation no doubt can be explained by the megacolon, which was also found. Retrograde pyelograms were made on the operative side October 13, 1952, and on March 13, 1953, an excretory urogram was taken (fig. 6). Fortunately sufficient function was present so that the kidneys and ureters could be visualized. The advantages of excretory urograms in a study of this type are of great importance. According to the Department of Roentgenology, there was a definite diminution in the size of the kidney and ureter on the operated side as compared with the unoperated side.

Both children feel fine. In the first instance it is extremely difficult to secure follow-up because of the feeling of well being, and in the second case the sub-

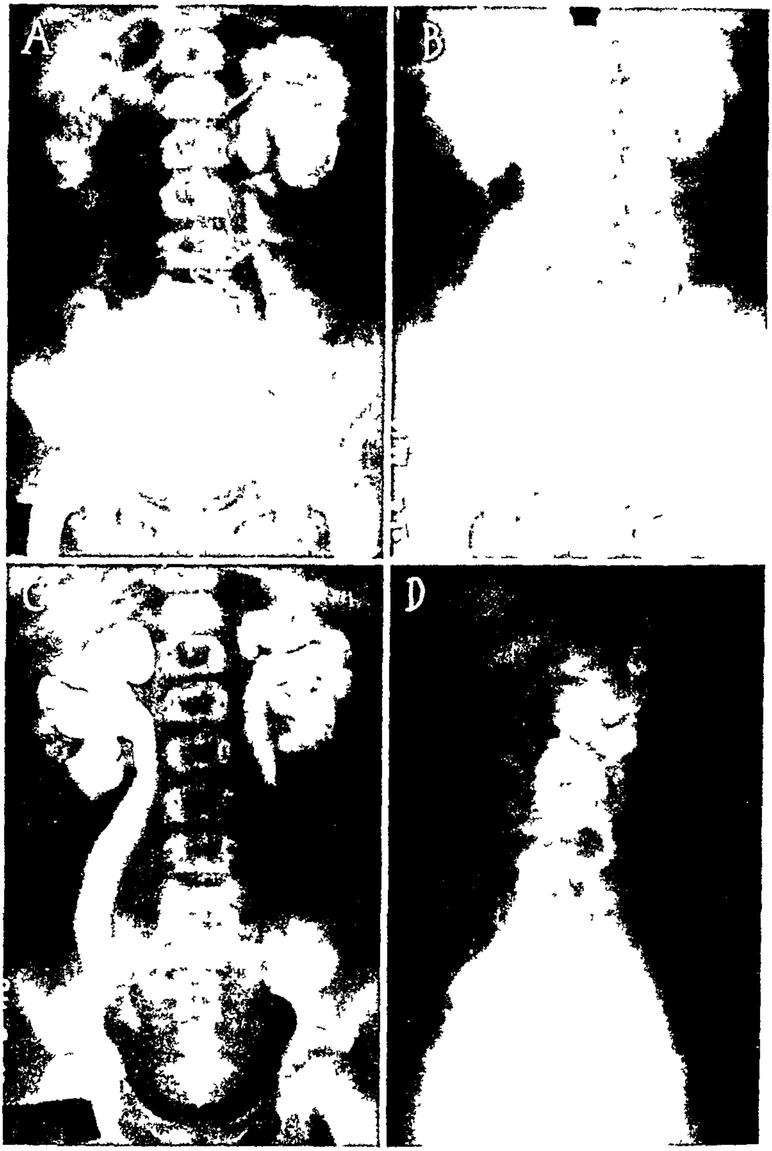

FIG. 6. *A*, pyelogram 6 weeks after intrapsoas transplant of left megalo-ureter. *B*, excretory urogram 6 months after operation. *C*, retrograde pyelogram 6 months after operation. *D*, lateral pyelogram showing position of ureter.

jective improvement in the child has made the parents so extremely grateful that follow-up should be no problem.

SUMMARY

A new operation for megalo-ureter is presented consisting of the transplantation of the dilated ureter into a trough made by splitting the psoas muscle. The activity of the psoas muscle in daily living should stimulate the ureter to improved function.

The trough should be both as deep and as long as possible and should extend from the renal pelvis to within one or two centimeters of the bladder.

The psoas muscle should be tightly closed over the ureter with interrupted sutures of chromic catgut and the psoas fascia approximated. The kidney should be suspended to prevent angulation of the ureteropelvic junction.

Two children, both girls, are presented with bilateral megalo-ureters, each of approximately the same grade on either side. In each instance one side was operated upon and the other side was left as a control.

The results of the operation may be regarded to have some merit, although conclusive results have yet to be obtained and further cases are needed.

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TABLE 1—*Continued*

CONTRACTION	RELAXATION	BY STIMULATION OF	ANIMAL	AUTHOR[1]	DATE
Base of Bladder		Hypogastric nerves	Dog	Elliott Fagge	1907 1902
			Cat, Dog	Debaisieux[7]	1912
		Distal cut end hypogastric nerves	Cat	Dale Langley & Anderson[7]	1906 1894
			Dog	Hanč	1898
Base of Bladder →	Bladder[5]	Hypogastric nerves	Cat	Dale Edmunds & Roth Lewandowsky	1906 1920 1900
		Distal cut end hypogastric nerves	Cat	Barrington Elliott	1915 1907
			Cat, Dog	Langley & Anderson	1895
		Anterior roots of lumbar spinal nerves	*Cat, Dog*	*Langley & Anderson*	*1895*

cut ends. Courtade and Guyon (1896) believed that the contraction which resulted from excitation of intact hypogastric nerves was solely a reflex phenomenon. Elliott ('07), and Griffiths (1894) always sectioned the hypogastric nerves and stimulated their distal cut ends to avoid reflex changes. Stewart (1899a, 1899b) observed no difference in unilateral stimulation of an intact or sectioned nerve except that excitation of the former caused a passive bulging on the contralateral side. The majority of the workers, among them Kuntz and Saccomanno ('44), and Langley and Anderson (1894, 1895) found no essential difference in the response obtained from stimulation of intact nerves or of their peripheral cut ends. See table 1.

Most workers believe that a hypogastric nerve supplies only the corresponding side of the bladder. A strictly unilateral response was observed by Griffiths (1894), and Stewart (1899a), upon excitation of the distal cut end of a hypogastric nerve. See table 1. Sherrington (1892) obtained a similar result following stimulation of anterior lumbar roots of spinal nerves. Debaisieux ('12), MacDonald and McCrea ('30), and Langley and Anderson (1894) reported a slight contraction on the contralateral side in addition to the usual homolateral response. After an extensive review of the literature Gruber ('33) came to the conclusion that the bladder response evoked on excitation of the distal cut end of a hypogastric nerve was limited in its effect to the corresponding half of the viscus and affected equally all portions of the detrusor muscle.

It is apparent that there is need for more precisely determined information on the pattern of response evoked by activity of the sympathetic outflow.

Previously, using the method devised for measuring the regional activity of the bladder (Hegre and Ingersoll, '49), it was found that all regions of the bladder participate in the diphasic response following bilateral stimulation of the sympathetic outflow and, in addition, that all portions of the viscus exhibit spontaneous activity (Ingersoll and Hegre, '51). The present study was undertaken to ascertain the behavior of the detrusor muscle in response to unilateral stimulation of hypogastric nerves.

METHODS

Adult cats, anesthetized with 20 mg. Dial (Ciba) and 50 mg. chloralosane (per kg, i p.), were used. Following a midventral abdominal incision to expose the hypogastric and pelvic nerves the bladder was rotated so that the posterior surface was uppermost. On this surface were placed small squares of white adhesive paper each bearing a small black spot in its center. The paper squares were arranged so as to divide this surface into quadrants and segments (fig 1) By means of a Ciné-kodak Special 16 mm. camera, mounted above the bladder, photographs were taken at 1 sec. intervals during the course of each observation. Subsequently, by projecting the film onto suitable paper, measurements were made and the results plotted of the activity taking place per unit length of muscle in each segment during each sec. of observation. In addition, a kymograph record was kept of the total bladder response under conditions of constant pressure (Hegre and Ingersoll, '49). A square wave stimulator (Grass) was used in all experiments with the instrument set to discharge at a frequency of 20–30 per sec, a 2 msec. delay and at a duration rate of 5 msec.

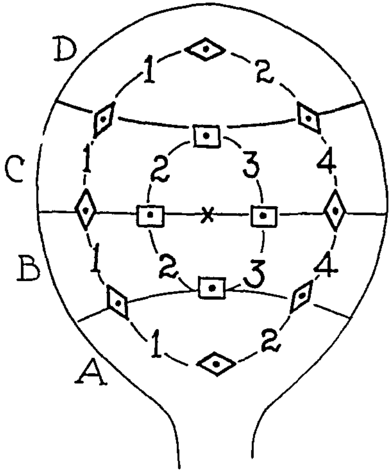

Fig 1 Schematic drawing of exposed surface of bladder showing location of quadrants and segments

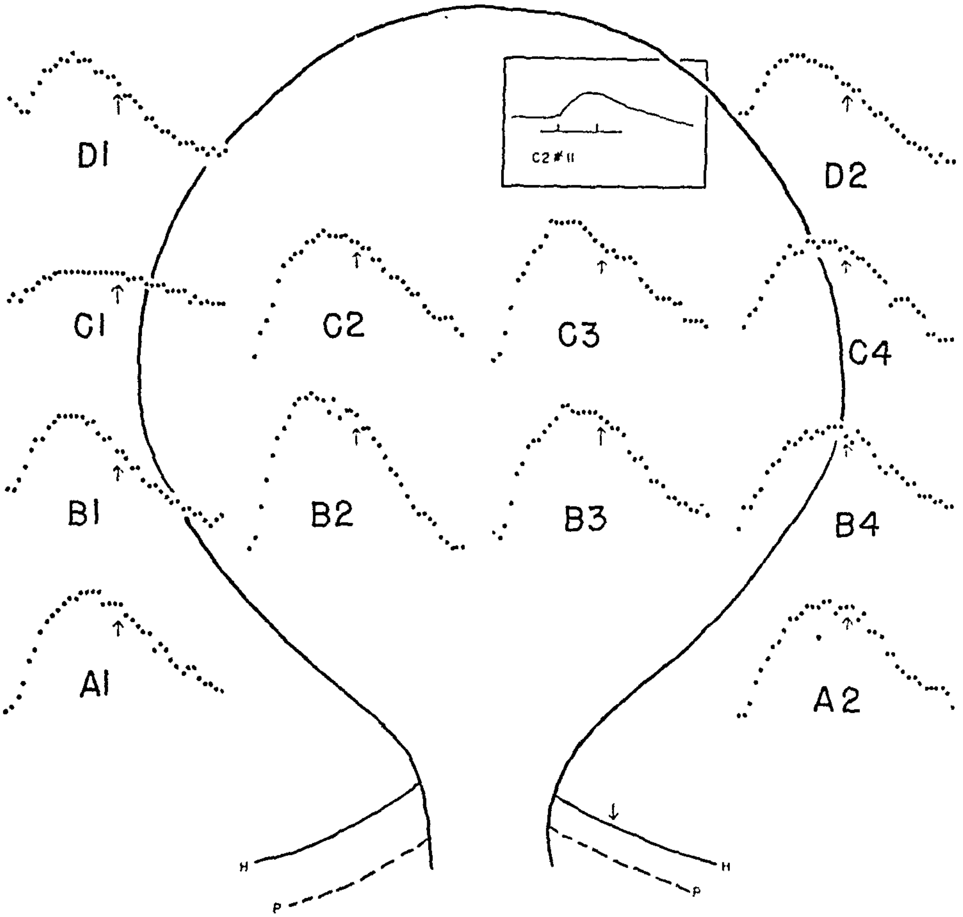

FIG. 2. *Bladder responses in cat 2, exp. 11. Unilateral stimulation of a hypogastric nerve with all nerves to the bladder intact. Intravesical pressure held constant at 14 cm. water.*

Figures 2–7 are graphic records of muscle activity taking place in each bladder segment in response to unilateral stimulation of hypogastric nerves. Each circle represents activity taking place during each second of observation. Onset of stimulation coincides with first circle of each curve while cessation of stimulation is indicated by an upward pointing arrow (except in fig. 7, upper curves, where period of stimulation was 59 sec.). A downward pointing arrow indicates side of bladder stimulated. A cross-bar through a nerve indicates section of that nerve. Insert: kymograph record of each observation, together with the time of stimulation. Abbreviations: H, hypogastric nerve; P, pelvic nerve; A1, A2, B1, etc., bladder segments.

RESULTS

1. *Effect of unilateral stimulation of hypogastric nerves with all nerves to the bladder intact.* Unilateral stimulation resulted in a prompt diphasic response of the detrusor muscle on the corresponding side (figs. 2, 3, 4). The period of initial contraction lasted from 8 to 15 sec. and was followed immediately by relaxation in the same regions.

On the contralateral side several types of responses occurred. The one most frequently observed was similar to that recorded on the stimulated side. In some instances the initial contraction was very brief and was followed by a prolonged relaxation (fig. 3, D1, upper curve; fig. 4, B1, upper curve). Another type of response had a latent period of 1 to 3 sec. before the onset of contraction (fig. 3,

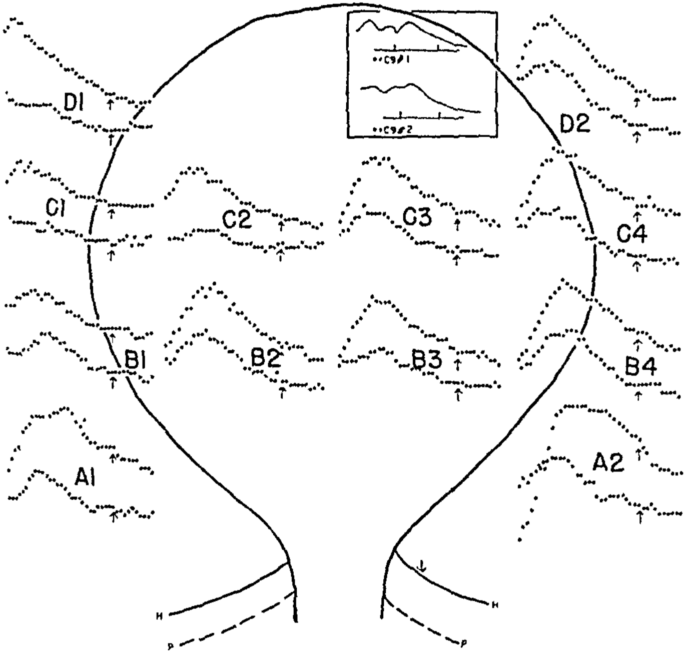

FIG. 3. Bladder responses in cat 9. Unilateral stimulation of hypogastric nerves with all nerves to the bladder intact. Upper curves, closed circles (exp. 1), right hypogastric nerve stimulated; lower curves, open circles (exp. 2), left hypogastric nerve stimulated. Intravesical pressure held constant at 16 cm. water.

A1, lower curve; fig. 4, C1, upper curve and B2, lower curve). In some regions the detrusor muscle relaxed during this period of initial delay (fig. 2, D1; fig. 4, C2, upper curve). In the remainder of the responses relaxation of the detrusor was pronounced and occurred without the usual initial contraction (fig. 3, C1, D1, lower curve; fig. 4, B1, C1, C2, D1, lower curve).

The amount of initial contraction per unit length of muscle, following unilateral stimulation of intact nerves, showed considerable variation. In one experiment (fig. 8, C2 No. 11) the average amount of contraction in the homolateral and contralateral halves of the viscus was about equal, while in the other studies in this series (fig. 8) marked differences were evident. In two observations from cat 9 stimulation of the right hypogastric nerve (C9 No. 1) elicited a greater response than when the left nerve was excited (C9 No. 2). Similar studies in cat 4 (C4 No. 2, C4 No. 4) also evoked contrasting reactions. Relaxation without previous contraction was a notable feature on the contralateral side in two of these bladder studies (C9 No. 2; C4 No. 4).

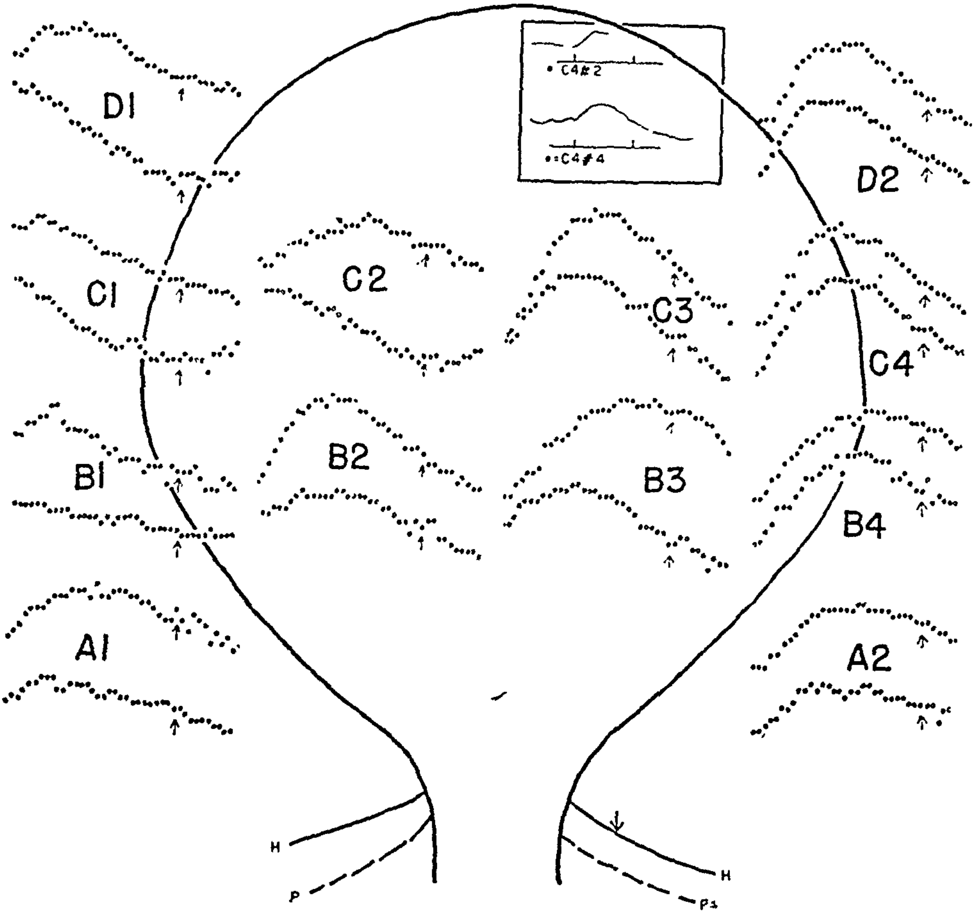

FIG. 4. Bladder responses in cat 4. Unilateral stimulation of hypogastric nerves with all nerves to the bladder intact. In upper curves, closed circles (exp. 2) left hypogastric nerve stimulated; in lower curves, open circles (exp. 4) right hypogastric nerve stimulated. Intravesical pressure held constant at 27 cm. water.

2. *Effect of unilateral stimulation of intact hypogastric nerves after section of the pelvic nerves.* Unilateral stimulation of an intact hypogastric nerve following section of the pelvic nerves gave a prompt and unusually vigorous response in all regions of the corresponding half of the viscus (fig. 5). On the opposite side similar responses were noted in segments A1, D1, B2, while in the other areas contraction occurred after a short latent period. The amount of contraction per unit length of muscle was considerably greater on the stimulated side than on the opposite side (fig. 9, C9 No. 11).

3. *Effect of unilateral stimulation of the distal cut end of a hypogastric nerve with the opposite hypogastric nerve intact and with the pelvic nerves sectioned.* The response on the stimulated side (fig. 6) was a prompt contraction followed by relaxation. On the opposite side all portions of the detrusor muscle exhibited an initial contraction which was followed by relaxation in the same regions but most of the responses were weak or were delayed 1 to 3 sec.

The average amount of contraction per unit length of muscle was much greater on the stimulated side than on the opposite side (fig. 9, C9 No. 13).

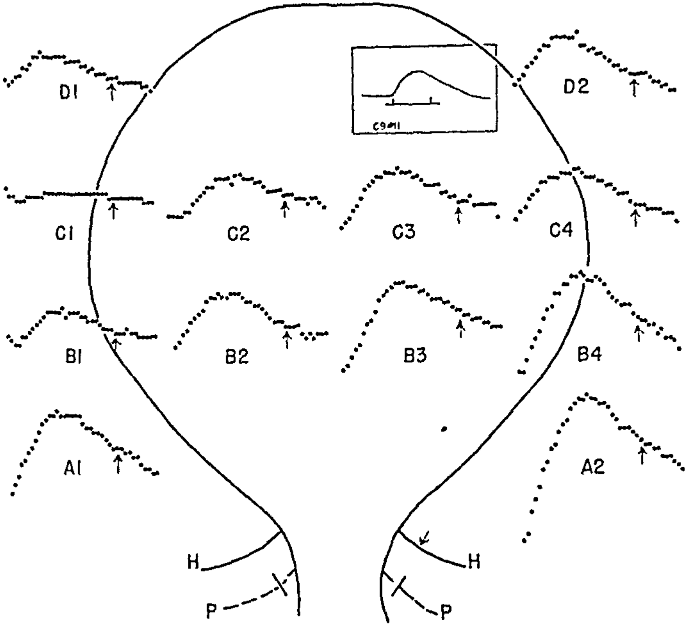

FIG 5 Bladder responses in cat 9, exp 11 Unilateral stimulation of right hypogastric nerve with pelvic nerves sectioned All hypogastric nerves intact Intravesical pressure held constant at 11 cm water

4 *Effect of unilateral stimulation of the distal cut end of a hypogastric nerve with the opposite hypogastric nerve and the pelvic nerves sectioned* The two studies (fig 7) are from the same cat and differ from each other only in the side stimulated (right nerve, C9 No 19, left nerve, C9 No 16) In both observations contraction occurred in all homolateral and in many contralateral segments This response was often delayed or was preceded by an initial relaxation on the contralateral side

The amount of contraction per unit length of muscle following stimulation of the distal cut end of the left hypogastric nerve (fig 9, C9 No 16) was about the same on both sides of the bladder Stimulation of the distal cut end of the right hypogastric nerve (fig 9, C9 No 19), however, evoked a much greater contraction on the stimulated side than on the opposite side and, in addition, the overall contraction was more vigorous when compared to stimulation of the left nerve

DISCUSSION

Data have been presented showing that unilateral stimulation of hypogastric nerves elicited responses, not only on the corresponding side, but on the opposite

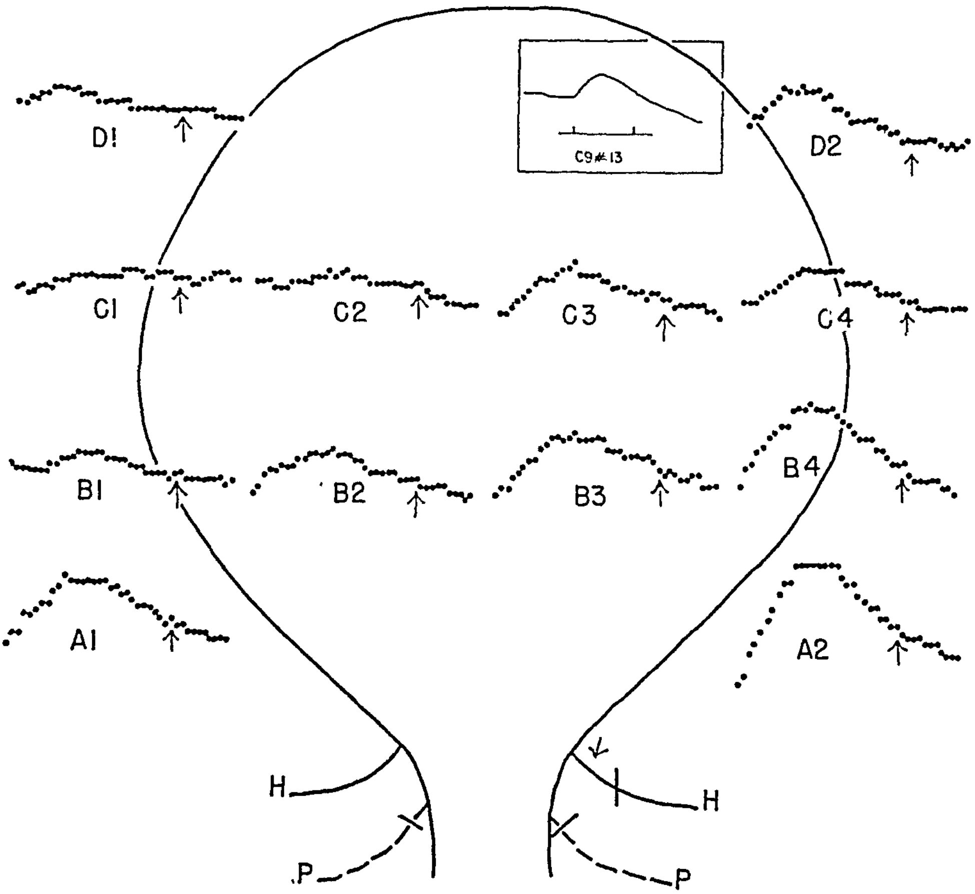

FIG. 6. Bladder responses in cat 9, exp. 13. Unilateral stimulation of distal cut end of ht hypogastric nerve with pelvic nerves sectioned. Left hypogastric nerve intact. Intrasical pressure held constant at 11 cm. water.

le of the bladder as well. On the stimulated side there always was a reasonably ompt contraction of the detrusor muscle which was followed usually by relaxan in the same regions. No particular area on the stimulated side could be said be more active than any other region.

On the contralateral side of the viscus unilateral stimulation evoked more an one type of response. Slightly over half were similar to those observed on e stimulated side. In some regions, especially near the fundus, the contractions ere of extremely short duration and were usually followed by prolonged relaxan. Another type of response recorded from the contralateral side had a latent riod of from 1 to 4 sec. before the onset of contraction. As a rule, the contracn when it appeared was vigorous and was followed by the customary relaxan. Sectioning of the nerves and stimulation of their distal cut ends had a ndency to delay the onset of contraction. In a few regions the initial contracn was preceded by a very brief relaxation. In other areas this relaxation persted throughout the period of stimulation.

The amount of contraction per unit length of muscle varied within wide limits the same and different bladder studies. In one series of observations from the

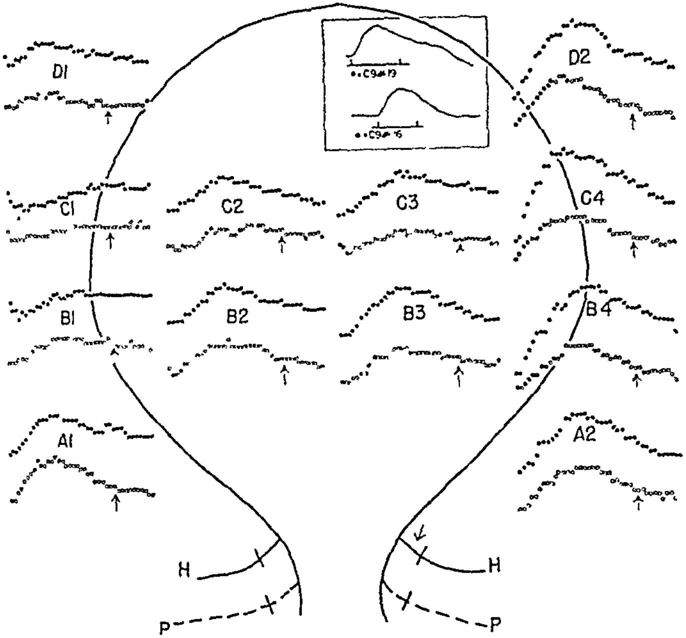

Fig 7 Bladder responses in cat 9 Unilateral stimulation of distal cut end of left hypogastric nerve in exp 16 (lower curves, open circles), and of distal cut end of right hypogastric nerve in exp 19 (upper curves, closed circles) Pelvic nerves sectioned Intravesical pressure held constant at 11 cm water

same cat (C9) stimulation of the right hypogastric nerves regularly elicited a greater contraction, in both halves of the viscus, than stimulation of the hypogastric nerves on the left side This held true following excitation of intact nerves or of their peripheral cut ends In two studies from another cat (C4) similar results were recorded In all of the studies, irrespective of the side stimulated, the average amount of contraction on the homolateral side always exceeded, though sometimes only slightly, the average amount of contraction obtained from the contralateral side The least responsive areas in any single observation were always on the contralateral side, generally along the lateral margin and adjacent to, or within, the fundic portion of the viscus

One factor which was thought by many workers to influence the amount of contraction and subsequent relaxation was the intravesical pressure at the onset of stimulation McCrea and MacDonald ('34) regularly elicited inhibition of vesical activity upon stimulation of the hypogastrics at a good level of pressure They, as well as Mellanby and Pratt ('39), found that when the intravesical pressure was low, bladder contractions were obtained According to the latter investigators, if the pressure was then raised and the same stimulus applied, the

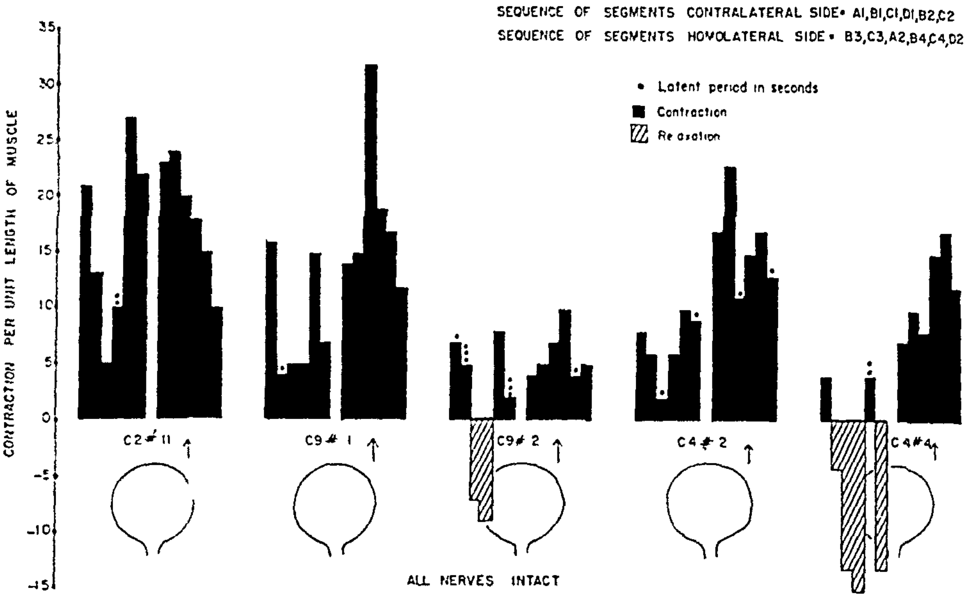

FIG. 8. Graphic representation (prepared from data in figs. 2–4) of the amount of contraction per unit length of muscle in millimeters in response to unilateral stimulation of hypogastric nerves with all nerves to bladder intact. Relaxation following contraction is not shown. Regional activity is grouped into homolateral (indicated by upward pointing arrow) and contralateral blocks. Sequence of segments in each of blocks is from left to right. Abbreviations as before.

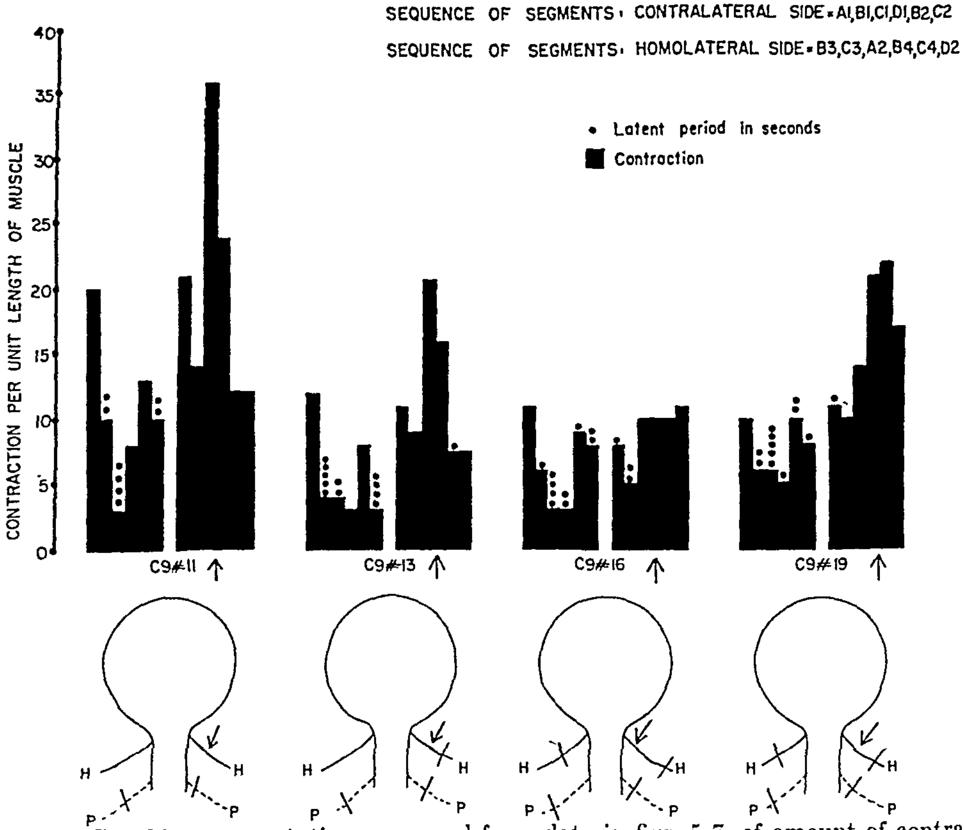

FIG. 9. Graphic representation, prepared from data in figs. 5–7, of amount of contraction per unit length of muscle in millimeters following unilateral stimulation of hypogastric nerves. Relaxation following contraction is not shown. Abbreviations as before.

initial contraction obtained was small and the subsequent relaxation large In our experiments the amount of pressure within the bladder seemed to have little effect upon the amount of contraction and subsequent relaxation but we did obtain marked differences in the amount of contraction by stimulating different sides of the same bladder. In a previous report (Hegre and Ingersoll, '49) evidence was advanced to show that the prestimulatory volume was of greater significance than the intravesical pressure in determining the amount of contraction and resulting relaxation.

The responses which have been obtained from unilateral stimulation of intact nerves and of their distal cut ends indicate a much more extensive bilateral innervation of the detrusor muscle than has been suggested heretofore. It is reasonable to assume from these data that all regions of the viscus are supplied by each hypogastric nerve. However, the richness of the supply is variable, not only to the contralateral side, but to the same side as well.

SUMMARY

Unilateral stimulation of hypogastric nerves always elicited on the corresponding side a prompt contraction of all portions of the detrusor muscle which was followed immediately by relaxation in the same regions.

On the opposite side slightly over one-half of the responses, following unilateral stimulation of hypogastric nerves, were similar to those observed on the stimulated side. Another group of responses had a latent period of from 1 to 4 sec before the onset of contraction. Sectioning of the nerves and excitation of their distal cut ends had a tendency to lengthen the latent period. In the remainder of the responses elicited from the contralateral side the initial reaction was one of relaxation. In some regions this was followed by contraction and subsequent relaxation; in others, relaxation was the only response.

The amount of contraction per unit length of muscle in response to unilateral stimulation varied within wide limits in the same and different bladders. Sectioning of the nerves or altering the intravesical pressure did not materially affect the result. The average amount of contraction on the homolateral side always exceeded that obtained from the opposite side The least responsive areas in any single observation were on the contralateral side, generally along the lateral margin and adjacent to or, within, the fundic portion of the bladder.

These studies indicate a much more extensive bilateral innervation of the detrusor muscle by hypogastric nerves than has been previously suggested. All areas of the bladder wall were found to be supplied by each hypogastric nerve but the richness of this innervation was quite variable, especially on the contralateral side, near the lateral margin of the viscus.

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STRIATED MUSCLE FIBERS OF THE VESICAL NECK

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Previous studies[1, 2] dealt with physiologic observations of the vesical neck following pudendal nerve anesthesia[1] and pudendal nerve stimulation.[2] These observations were explained on the basis of anatomical findings of intertwining smooth and striated muscle fibers at the bladder neck as reported in the literature.[3, 4a, b, 5, 6, 7] The purpose of our investigation was to confirm the presence of striated fibers in shavings obtained by transurethral resection, to endoscopically find their location and to examine them for possible pathological changes.

PROCEDURE AND RESULTS

Twenty-one patients were investigated. All but one, who had an epidural abscess, suffered from traumatic lesions of the spinal cord or cauda equina. Fifteen patients had upper motor neuron lesions and six had lower motor neuron lesions. Of the latter group, two patients had a secondary lower motor lesion following a subarachnoid injection of absolute alcohol for the treatment of skeletal spasticity and one had a degenerative lesion of the cord below his original level of T-9. Three patients with levels at C5, C6 and T5, respectively, had incomplete lesions, while the rest had physiological or anatomical transections. The spinal cord level ranged from C6 to L1 and the age from 19–44 years. The time interval between injury and vesical neck resection was from six months to two years in the majority of cases; four patients underwent surgery between 5 and 8 years, respectively.

The Stern-McCarthy and Baumrucker instruments were used for resection. The tissue was retrieved from the bladder neck proximally to the verumontanum.

The strips of resected tissue were submitted to the laboratory in bottles con-

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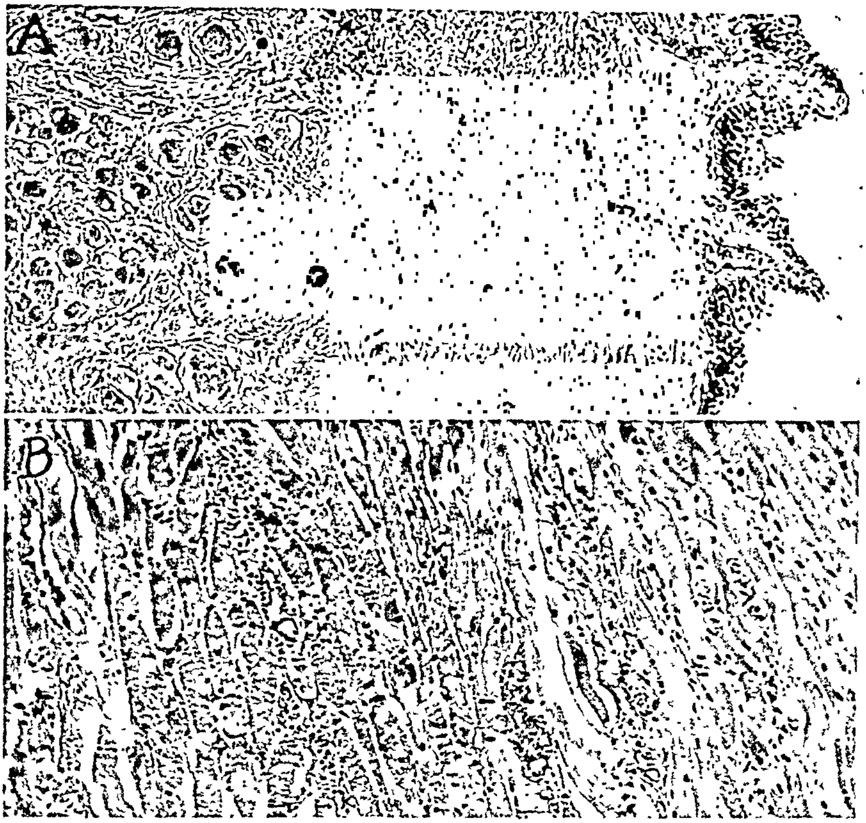

FIG. 1. A, section of vesical neck showing surface of transitional epithelium with underlying stroma, mildly infiltrated by lymphocytes. In deeper portion of section there are bundles of striated muscle, some in close proximity with bands of smooth muscle. B, sections of striated muscle. Mild interstitial edema and small collection of lymphocytes and histiocytes are present.

taining formalin and labeled according to a clock pattern, the code of which was unknown to the pathologist. The strips consisted of from six to approximately forty segments of grayish pink, irregularly smooth and rubbery tissue, the largest segments of which measured 2.0 by 0.5 by 0.5 cm; the amount of tissue varied from 1.8 to 5.2 gm. The tissue was embedded in paraffin and stained with hematoxylin and eosin; where necessary, special stains were used (Van Gieson, Masson, fat).

Microscopically, the segments of tissue consisted for the most part of fibromuscular (smooth muscle) tissue. Many of these strips showed edema and foci of lymphocytes and histiocytes. In segments of vesical neck (fig. 1, *A*) the mucosa consisted of flattened transitional epethelium and the stroma of moderately edematous connective tissue mildly infiltrated with lymphocytes. Underlying bands of smooth muscle were in close proximity to bundles of striated muscle which were lying deep in these strips. In other segments, bundles of striated muscle were separated by edema and collections of polymorphonuclear leukocytes, lymphocytes and histiocytes (fig. 1, *B*). In many areas the striated muscle was undergoing degenerative changes and early fibrosis (fig. 2, *A*). In still other segments, bundles of striated muscle were replaced and surrounded by fibrous tissue (fig. 2, *B*).

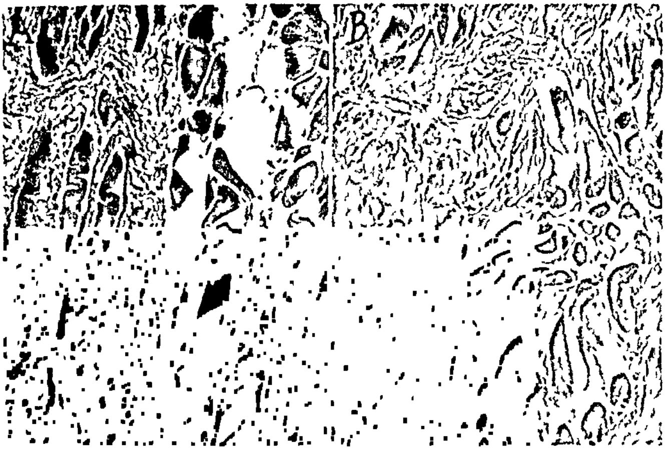

FIG 2. A, degeneration and mild fibrosis of striated muscle fibers. Artefactual shrinking of muscle substance from sarcolemma. B, bundles of atrophic striated muscle surrounded by bands of replacement fibrous tissue.

In all but two instances, striated fibers were demonstrated in the shavings of the anterior lip between 3 and 9 o'clock, while the posterior lip contained only smooth muscle fibers.

The clinical results of micturition of the 15 patients with upper motor neuron lesions were good in eight and poor in seven cases. In all eight, striated fibers were found in the anterior lip. Of the 7 cases, five did show evidence of resected striated fibers while two did not. Four of these 5 cases had a temporary good result (C7, C7, T7, T11), while the fifth (T1) never responded to the resection. Both cases, whose tissue examination failed to show striated fibers, were quadriplegics.

The results from resection were good in all six cases with lower motor neuron lesions and striated fibers could be demonstrated in all instances.

DISCUSSION

Anatomical descriptions of extension of striated fibers to the vesical neck are reported by Rochet[3] in 1899, Wesson[4a, b] in 1920 and 1950, Young and Wesson[5] in 1921, D'Arcy McCrea[6] in 1926 and Elliot[7] in 1952. These investigations, based upon gross and microscopic examinations of adult and embryologic specimens, indicate that striated fibers of the urethral sphincter mingle with smooth fibers close to the anterior urethral mucosa and contribute to the formation of a functional external bladder "sphincter." It is surprising that striated muscle fibers have not been found in the transurethrally resected tissue. This tissue was variously described by authors as: "fibromuscular prostatic hyperplasia,"[8] "adenofibromatous hyperplasia, inflammatory muscle, smooth muscle,"[9] "hypertrophy of muscle, fibrosis,"[10] "hyperplasia of muscle and inflammatory, adenofibromatous hyperplasia,"[11] and as "fibromuscular tissue, round cell infiltration in fibrous tissue."[12] The failure to mention striated muscles in the shavings is the more astounding as most authors recommend resection along the entire circumference[10, 13, 14, 15, 16, 17] and very few restrict their resection to a small localized area of the bladder neck.[18, 19] Some authors,[8, 14, 20, 21] however, have intentionally attacked the external urethral sphincter distally to the verumontanum by excision or electrofulguration, a procedure which, though purposeful and successful, differs anatomically from our operation.

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The recognition of the physiologic significance of an external bladder "sphincter"[22, 23, 24] led consequently to the endeavor to differentiate malinnervation of this "sphincter" from structural contracture by means of pudendal nerve anesthesia.[1] The previous observation of contraction of the vesical neck on stimulation of the pudendal nerve[2] finds further corroboration by demonstration of striated *muscle fibers in the presented slides and confirms the veracity of a hypothesis* which was based upon the work done by others.[3, 4a, b, 5, 6] These fibers are closer to the mucosal surface than suspected. They are of necessity innervated by a somatic nerve and consequently the pudendal nerve supplies motorically an area which extends through the anterior and lateral aspects of the prostatic urethra and includes at least the urethral slope of the anterior vesical lip.

Thus the theory of micturition of the adult, based upon roentgenologic observation,[25] receives additional support and the striated urethral sphincter cannot be considered to be a mere auxiliary muscle, because its muscular tone is significant for the respective condition of the detrusor. Since these structures

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receive a reciprocal innervation from the same cord segments, by somatic and autonomic fibers, respectively, the difference of micturition between infant and trained child can be better understood considering that training follows chronologically other manifestations of myelinization, e.g., walking.

The observed pathological changes of degeneration, inflammation and fibrosis of the striated fibers have a farther reaching functional implication because of the intimate proximity between striated and smooth muscles. Fibrosis leads eventually to structural contracture of the vesical neck, which can be corrected by a tenotomy-like procedure, in some cases, especially with lower motor neuron lesion, as little as 0.5 gm. of tissue will, if removed, make the difference between retention and voiding. Radical transurethral resections with removal of large amounts of tissue (more than 5.0 gm.) are unnecessary in patients with spinal cord injuries, since these individuals have notoriously small prostates (except older men with pretraumatic prostatic enlargement) and since it is the vesical neck rather than the prostate which causes the bladder imbalance.

In analyzing the results of our treatment in these twenty-one patients, the instability of a cord bladder[19] is again demonstrated in that 4 patients (three with lower and one with upper motor neuron lesions) needed resection, 5, 6 and 8 years, respectively, after injury.

As was to be expected according to the rationale of treatment, discussed elsewhere,[19] the results were more favorable in the 6 patients with lower motor neuron lesions than in the fifteen with upper motor neuron lesions. However, the continence of patients with lower motor neuron lesions is easily jeopardized, this was the case in one of the six patients after the removal of 5.2 gm. of tissue from the entire circumference. It should be possible to avoid this condition by a gradual resection, performed in several sessions.

Of the 7 patients with upper motor neuron lesions, who did not respond to resection, two were paraplegics and five were quadriplegics. Restoration of bladder function in quadriplegics is more difficult to achieve than in paraplegics, even auxiliary procedures fail readily in these patients, such as pudendal neurotomy or neurotripsy, because of the absence of volitional abdominal pressure or the use of hands, essential for bladder emptying after the pelvic floor has been paralyzed. Pudendal neurotripsies were done in two paraplegics with good results, in one quadriplegic with an equivocal result, micturition being unreliable, and in another quadriplegic with a poor result. Three other quadriplegics underwent pudendal nerve anesthesia but the result was either equivocal or the lesion (in two patients) too incomplete to justify destructive surgery of the pudendal nerves.

Our past experience during a five year period with 210 resections in 144 patients has taught us that in many instances a resection of the prominent posterior lip will suffice to restore function, this indicates that the structural contracture remained confined to smooth muscles. Only when this operation fails or when upper motor neuron lesions do not respond to pudendal nerve anesthesia, must one assume that additional contracture is caused by striated fibers, this condition then requires an extension of the resection to the anterior lip. Extreme caution is advisable in cases with lower motor neuron lesions; not to resect too much is the rule because these patients, who by virtue of their cord lesions tend to show stress incontinence, easily become completely incontinent. Primary complete resection around the entire circumference should be the exception rather than the rule in patients with cord injuries.

Why no striated fibers could be recovered in 2 cases from corresponding places where they were demonstrated in nineteen instances, is not understood. Explanations such as individual varieties or depth changes of the striated fibers, are offered as a mere conjecture.

The significance of striated fibers at the described location may be of interest to the urologist who treats, besides traumatic paraplegics, patients with obstructive uropathies. Incontinence after resection need not be due to direct trauma of the urethral sphincter distally to the verumontanum, but (that muscle) may be indirectly weakened by injury of striated fibers during the resection of the anterior prostatic commissure.

SUMMARY

A systematic histologic examination was done of transurethrally resected tissue from the vesical neck of 21 patients with spinal cord lesions.

This examination showed striated muscle fibers of the anterior circumference of the bladder neck and anterior vesical lip in nineteen of the 21 subjects.

Degeneration, infection and fibrosis were present in these fibers, which are located in close proximity to smooth muscle fibers and in shallow relationship to the mucosa.

The literature of anatomical studies is reviewed.

The significance of the findings is discussed for physiological and pathological bladder function.

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SCHISTOSOMIASIS OF THE URINARY BLADDER: WITH SERIAL BIOPSIES UNDER THERAPY

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Cases of parasitism by the diecious blood fluke of Bilharz, Schistosoma haematobium, have been rarely encountered by physicians practicing in the temperate zone. Modern transportation, however, has shortened the distance between the ancient endemic foci of this parasite, Egypt and adjacent areas, and the rest of the world. It therefore behooves the physicians in noninfected areas to be aware of this exotic disease and to have some knowledge of 1) its clinical and pathologic aspects, 2) diagnostic procedures, and 3) the most effective therapeutic measures.

Some fear has been expressed that this parasite might become endemic in other areas. Since its complex life cycle is dependent upon the existence of suitable molluscan hosts, the geographic distribution of S. haematobium is governed by the presence of certain nonoperculate snails (Bulinus, Physopsis, and possibly Lymnaea) (Belding; Craig and Faust; Faust, 1939; Mackie, et al; Strong), to which it is adapted. These genera of snails, for the most part, are common only in southern Europe, Africa, and western Asia; thus the possibility of extension of this blood fluke to other regions is somewhat remote.

Several other aspects of Schistosoma haematobium infection require comment. Faust (1939) estimates the life of the adult parasite in the human body at about twenty years; moreover, though the adult parasites may be killed with therapy, the pathologic reaction to the ova continues. The symptoms may be somewhat minimal for years, and the cure rate with the available drugs is not high (Cummings; Faust, 1939). These aspects prompt us to report this case.

Since the case reported by Peacock and Voegtlin (1935) is thought to be doubtful by Faust (1939), this apparently represents the first authentic case reported from the State of Washington.

CASE REPORT

A 20 year old white foreign seaman was admitted to the urological service of the U.S.P.H.S. Hospital, Seattle, Washington on August 22, 1952, complaining of bilateral flank pain of 5 months' duration. The pain radiated to the pubic region. During this time, he had an episode of painless hematuria which subsided in a few days. There was no history of injury or passage of calculi. Eight days prior to admission, he had frequency, urgency and dysuria which persisted. Past history revealed that the patient was of Greek extraction, born in Egypt, but had resided in Australia since childhood. Even though working as a seaman for the past 4 years, he presented no history of exposure to infection. The family history was irrelevant. He had the usual childhood diseases with no sequelae and

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had been in relatively good health during young adult life. There had been no operations or injuries. System review failed to reveal any pertinent information.

Blood pressure, temperature, pulse and respiration were within normal limits. The average weight was 176 pounds, but the weight on admission was 144. Part of his weight loss could be explained in that his captain suspected appendicitis and withheld solid foods. Except for lower abdominal tenderness on palpation, the physical examination was normal.

Excretory urograms revealed normal-appearing kidneys. No calculi were identified. Dye excretion was normal on both sides in 5 minutes. The left pelvis showed a somewhat bizarre appearance which was thought to be a normal anatomical variation. There was some dilatation, assuming an "S-shaped curve", of the lower ureter on the left. The dorsal and lumbar vertebrae showed no changes.

On admission the hemogram was within normal limits. The Kahn Standard was negative. The urinalysis was normal. Subsequent microscopic urinalyses showed erythrocytes because of cystoscopies and biopsies of the bladder. Culture of the urine showed no growth. Three 24-hour urines for acid-fast culture were reported as negative on Lowenstein's, Petragnani's and cooked blood agar media. Stool examinations showed an occasional Giardia lamblia cyst.

Eosinophil counts of the blood were made during the course of the disease and treatment. On September 12, 1952, the white count was 8,000/mm. with 16 per cent eosinophils.

Total circulating eosinophil counts* were as follows:

9/12	680/mm.		10/24	600/mm.	
9/13		Fuadin	10/27	481/mm.	
9/17	970/mm.	Fuadin	10/29	375/mm.	
9/19	1054/mm.	Fuadin	10/30	487/mm.	
9/22	1012/mm.	Fuadin	10/31	544/mm.	
9/24	900/mm.	Fuadin	11/5	463/mm.	
9/26	624/mm.	Fuadin	11/7	500/mm.	
10/1	875/mm.	Fuadin	11/10	260/mm.	
10/6	562/mm.	Fuadin	11/12	360/mm.	
10/3	626/mm.	Fuadin	11/14	218/mm.	
10/8	745/mm.	Fuadin	11/18	330/mm.	(Hetrazan)
10/10	533/mm.	Fuadin	11/19	325/mm.	(Hetrazan)
10/13	737/mm.	Fuadin	11/21	231/mm.	(Hetrazan)
10/15	581/mm.	Fuadin	11/24	250/mm.	(Hetrazan)
10/17	678/mm.	Fuadin	11/26	330/mm.	(Hetrazan)
10/18		Fuadin	11/28	206/mm.	(Hetrazan)

Examination of urine for ova and miracidia was negative on September 13, when Fuadin† therapy was instituted. Miracidia were seen on only two days, September 16 and 17 (fig. 1,*A*).

Ova were seen on the two succeeding days, September 18 and 19 (fig. 1, *B*). No parasites were found on September 30, October 2 and 7. A culture of the urine on October 2 revealed Escherichia coli. Daily urinalyses from October 14 through October 23 and October 27 through November 6 failed to demonstrate the parasite. Final urinalysis on November 25 was within normal limits.

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* Normal range in this laboratory, 200–300/mm.

† Winthrop Stearns, 6 per cent stibophen.

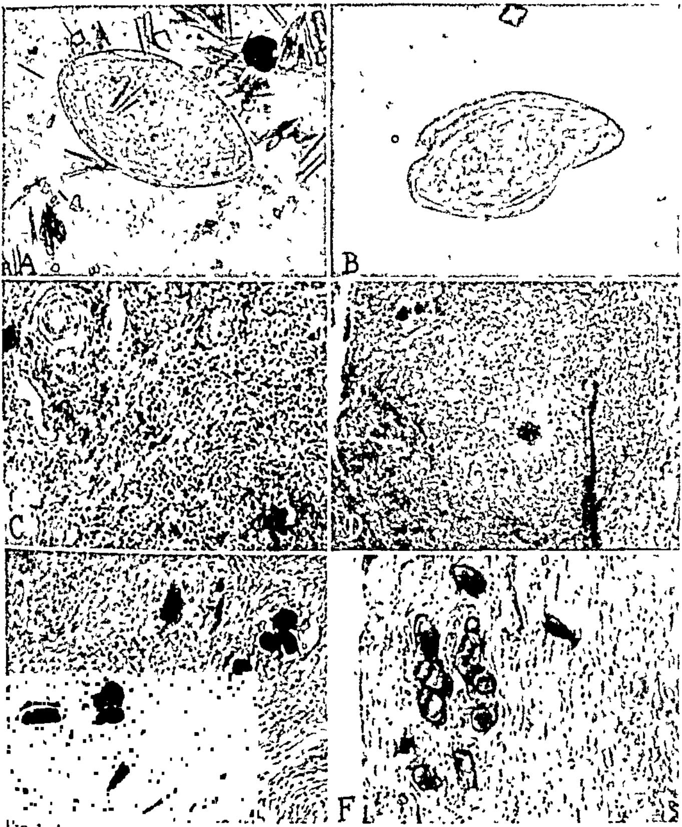

FIG 1. *A*, ovum of S. haematobium lying amidst calcium oxalate crystals. Terminal spine well shown *B*, miracidium appears breaking through shell of ovum. *C*, first biopsy to show ova (September 9, 1952). Note acute reaction. Main infiltrating cells are eosinophils. Beginning vascular proliferation is seen. *D*, intense response with necrosis in center was ringed by band of proliferating connective tissue cells with sparse to moderate infiltrate similar to *C* and outer ring of intense cellular infiltration. *E*, October 29, 1952, subacute reaction with beginning calcification of ova. Distinct terminal spine is seen at upper center. *F*, final biopsy November 17, 1952 Mucosa has been desquamated. Lesion progressing to chronic stage.

On August 29, 1952, cystosopy revealed bladder mucosa that appeared to be inflamed in spotty areas. These were composed of a small yellow center surrounded by a pearly gray border with a circumferential inflammatory reaction. The lesions were submucosal and measured 1–2 mm. in diameter.

Schistosomiasis was suspected and a biopsy was taken of one area. Although the left ureteral orifice was edematous, clear urine was seen flowing freely from both. The pathologic report from the first biopsy showed no schistosome ova.

On September 9, 1952, cystoscopy again disclosed infected mucosa with multiple yellow follicles in the posterior and lateral aspects and the base of the bladder. A biopsy confirmed the diagnosis of schistosomiasis. Subsequent examination on October 29, 1952 revealed that the reaction had not completely subsided. The biopsy on this occasion showed Schistosoma present in the bladder mucosa. On November 17, cystoscopy showed several areas of reaction still present and several small elevated lesions remaining. Biopsy again showed ova.

When the diagnosis of schistosomiasis of the bladder was made, the patient was placed on a course of Fuadin. This consisted of an initial daily intramuscular injection of 1.5 cc, 3.5 cc and 5 cc, followed by 5 cc every other day for 16 doses. A rest period of 2 weeks ensued. Even though improvement was noted, bilateral flank pain persisted. Examinations for ova during the rest period were negative. Because of the persistence of symptoms, Hetrazan* therapy was given for two weeks. The patient became asymptomatic and was discharged fit for duty to rejoin his ship. Adequate follow-up for five to ten years was advised.

Pathology: The bladder biopsy of August 29 showed mild chronic cystitis. There was a slight eosinophil infiltration.

The subsequent biopsy of September 9 revealed the ova of S. haematobium. The ova appeared with distinct terminal spines when the plane of section was proper to include this feature. The shell had been folded and retracted by fixation. The internal structure was composed of small basophilic nuclei nestled in basophilic granular amorphous material. In many instances this had also been differentially shrunken by fixation. Occasionally, medium to large cells with a vesicular nucleus and a pale eosinophilic, slightly granular cytoplasm with indistinct cytoplasmic boundaries were seen to lie immediately inside the shell. The presence of these ova had provoked three histologic pictures in the immediately surrounding tissues: 1) A group of ova lay in proliferating connective tissue with a sparse to moderate eosinophil infiltration. This was admixed with mononuclear cells and sparse numbers of neutrophils. The infiltration was quite intense immediately surrounding the ova and then became moderate for a small distance. An intense ring of infiltrate was seen at the periphery of the reaction (fig. 1, *C*). 2) An intense response with necrosis in the center was ringed by a band of proliferating connective tissue cells with a sparse to moderate infiltrate similar to the foregoing and an outer ring of intense cellular infiltration (fig. 1, *D*). Biopsy (September 9, 1952), necrotic tuberculoid type of reaction. 3) This type was much older. The ova were surrounded by giant cells of the foreign body type and lay in little masses in dense fibrous tissue. Cellular infiltration was extremely sparse and limited to a few monocytes and lymphocytes. Occasionally, this reaction presented a center of brightly eosinophilic, smudged material. All of these reactive foci lay in the submucosa which was edematous and thickened. There was a scant infiltration of eosinophils, monocytes and lymphocytes. An associated vascular reaction in the small vessels was manifested by slight to moderate intimal hyperplasia. The adventitia was also active, one vessel presenting an adventitial cell in mitosis. The mucosa presented some infiltration with eosinophils.

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* Lederle Laboratories Division, American Cyanamide Co., Diethyl Carbamazine 50 mg tablets. Hetrazan was used empirically. Its efficiency cannot be determined since improvement was noted during Fuadin therapy.

Resolution of the lesion had begun in the biopsy of October 29 and the intensity of the reaction had quieted markedly (fig. 1, *E*). The ova were calcifying. Some of the ova were completely calcified while others were in early stages with remnants of internal structure being seen. Foreign body giant cells were plentiful in juxtaposition to the ova. The fibroblastic proliferation was now replaced by more mature collagenous tissue. This had served to compress the ova-containing foci. Only scattered eosinophils were noted. The infiltrate, though sparse, was composed of lymphocytes and monocytes. The vascular reaction was subsiding. There remained some slight medial thickening and an occasional plump endothelial cell.

The healed fibrotic stage (fig. 1, *F*) was seen in the last biopsy. At this stage the ova appeared to be completely calcified. There was dense fibrosis of the submucosa surrounding the masses of calcified ova. A similar reaction was present in the areas of muscular involvement. Only a few scattered cells were noted; these were predominantly lymphocytes and monocytes. Eosinophils were a rarity. One section showed small nests of transitional epithelium beneath the surface as though chronic cystitis were developing.

DISCUSSION

The patient was referred to this hospital with a diagnosis of urinary calculus. The first inkling of his actual disease came from cystoscopy. The cystoscopic appearance of this lesion has been termed characteristic (Maker quoted Riba, Campbell, and Cummings). Gelfand emphasizes that a normal appearance of a bladder on cystoscopy does not rule out schistosomiasis and biopsy should be done. As the therapy progressed, the eosinophil count decreased. With the known vagaries of eosinophil counting, the relative fluctuations are not considered of importance. Although the eosinophil count is usually elevated, some cases do not show this feature (Goldey; Miller). This patient entered with bilateral flank pain.Excretory urograms showed an S-shaped dilatation in the lower left ureter. Edema of the left ureteral orifice was present on cystoscopy. Gelfand considers these findings significant in patients known to have schistosomiasis. Perhaps this patient had ureteritis concomitant with cystitis, although retrograde studies were not done to confirm this.

Because of the long life of the parasite, it is difficult to state where the infection of this seaman, of Egyptian nativity and Australian residence, occurred. The patient definitely stated that he had symptoms for only 5 months with one bout of hematuria during that time. He denied having hematuria at any previous time.

The finding of the characteristic ova or miracidia in the urine is diagnostic. However, Sayegh points out that 653 people suffering form S. haematobium infection were seen at the American Hospital in Tanta, Egypt in a two year period, yet parasites were not demonstrated in their urine. In our case, no ova or miracidia were seen before therapy was begun and then only on four successive days. For this reason cystoscopy and biopsy are probably the most efficient and quickest methods for making the diagnosis. In fact, Gelfand and Sayegh recommend that the biopsy material be crushed between two slides and examined under subdued light. More than one examination may be necessary to establish the diagnosis.

There is some indication in the second biopsy that more than one shower of ova had become implanted in the bladder as lesions of different ages were seen. This is characteristic of the infection as long as the adult parasites are alive. The biopsies themselves show the classic picture of the disease as given in the major texts in this field (Belding; Craig and Faust; Faust, 1939; Mackie, et al; Strong). However, none of the authors gave a time relationship between the stages, either with or without treatment. The resolution of the acute lesion to the chronic fibrotic type of reaction is presented. These are oriented in point of time with the Fuadin therapy. It is interesting to note that the gradual disappearance of eosinophils from the blood was coupled with their disappearance from the tissue. The vascular reaction has been thoroughly studied and Belding, quoting Koppish, mentions that the penetration of the ova into the tissues is accomplished, in part, by pressure and an endothelial and subendothelial reaction in the vessels. The reaction of the host tissue to the ova is said to be due, initially, to lytic secretions from the miracidia within the egg shell (Belding; Faust, 1948). Diffusion explains the circular configuration of the lesion in the beginning (Faust, 1948). The subsequent picture is that of a foreign body reaction. Calcification is the usual fate of an ovum. Dense fibrosis and contracture wall off the offending foreign matter. These lead to dysfunction of the organ in which they are taking place. In this regard, an article by Sayegh is most interesting.

When the diagnosis is made, treatment may be carried out with tartar emetic or stibophen (Fuadin). Therapeutic schedules are carried in the major texts (Belding; Craig and Faust; Faust, 1939; Mackie, et al; Strong) on this subject. The success of therapy may be judged, either by finding viable or nonviable ova in the urine or by biopsy of the bladder showing calcification of the ova and resolution of the acute reaction by fibrosis and contracture. Faust (1939) and Cummings comment that the relapse rate with Fuadin and tartar emetic is high and multiple courses may be necessary. Cummings maintains that a five to ten year follow-up is necessary from the standpoint of the infection. The residua from infection may not make themselves known for many months or years, especially if the infection is light (Miller).

The existence of potential reservoirs of this disease in our armed forces, merchant mariners, foreign seamen and travelers for business and pleasure may well present this lesion and its late complications to any of us for diagnosis and treatment.

SUMMARY

A case of Schistosoma haematobium of the bladder and probably left ureter is presented.

This is probably the first authentic case reported from the State of Washington.

Resolution of the lesion under Fuadin therapy as revealed by serial cystoscopic biopsies is discussed

The useful diagnostic procedures are outlined.

The necessity of long term follow-up is indicated.

The ever-present problem of schistosomiasis presenting in the United States and Canada is noted

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TUMORS OF THE BLADDER: SURVEY OF 180 PATIENTS

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Many urologists throughout the country are advocating radical surgery for the treatment of bladder tumors, regardless of the extent of the tumor or the pathological diagnosis. The reasoning behind a trend to early total cystectomy is based on two factors: 1) that the clinician cannot ascertain by clinical judgment whether or not a given bladder tumor, regardless of its size, configuration or location, will at some later date invade and kill the patient, and 2) that the pathological diagnosis is not reliable in determining the tumor's future growth and behavior.

The reason for this report is to show by careful investigation and long-term patient followup of tumors, which an experienced urologist diagnoses as clinically noninvasive, that very satisfactory results are obtained on a conservative surgical management. Total cystectomy and ureteral transplantation must be regarded as a very radical, and, in most instances, a debilitating procedure, and one which we believe should be reserved for patients with bladder tumors that are clinically and pathologically invasive.

METHOD

In this study, which includes the investigation of all applicable bladder tumor patients at Wesley Memorial Hospital from 1942 to 1952, the initial admission chart was carefully scrutinized for all pertinent information, and each additional admission chart checked for further helpful data. Next, the office records of these patients were thoroughly investigated to check the patient's status as to recurrences, treatment and general state of health for the followup. Finally, letters were sent to all patients who had not been seen recently to enable us to follow through with as complete a survival record as possible.

Herein we present a summary of the data extracted, with emphasis on survival.

GENERAL DATA

Of the two hundred or so case records studied, 180 patients with bladder neoplasm were acceptable for this investigation. On a few patients, sufficient information was lacking for proper inclusion. Sixty-five per cent of the patients were males and 35 per cent females (table 1). The disease developed in the majority between 60 and 70 years of age, about one-fourth were between 50 and 60, with lessening percentages from those ages down to small numbers in the third and ninth decades. The age range table illustrates this spread in percentage form.

As would be expected, most of the patients (87 per cent) had gross or microscopic hematuria, which most frequently first brought them to the urologist. Over half of the cases (55 per cent) had symptoms of bladder irritability such as frequency and/or nocturia. Nearly 40 per cent had some degree of pain or burning

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* Assisted by William Price, M.D.

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TABLE 1

Number of cases—180 Males—117 (65%) Females—63 (35%)

Age Range

20–30	30–40	40–50	50–60	60–70	70–80	80–90
1.3%	5.0%	8.3%	25.5%	42.7%	14.4%	2.8%

Complaints:				
Hematuria	87%	Frequency & nocturia	55.5%
Dysuria	37.7%	Suprapubic pain	8.3%
Flank pain	5.0%	Pyuria	1.0%

TABLE 2

Duration of symptoms when first seen:

0–3 mo	3–6 mo.	6 mo–1 yr.	1–2 yrs.	2–3 yrs	3–4 yrs	4–5 yrs	Over 5 yrs
43.0%	9.4%	20.0%	6.0%	6.0%	2.0%	2.0%	6.0%

Unknown—5.6%

G.U tract disease secondary to bladder tumor:		
	Hydronephrosis	22%
	Pyelonephritis	5%
	Fistulas	1%

Associated benign prostatic hyperplasia—33% of males

on urination. A much smaller number had suprapubic or flank pain, and still fewer suffered from pyuria.

We believe that an important factor in controlling bladder tumors is the promptness with which the patient seeks initial diagnosis and treatment and the subsequent attention he gives to his bladder health through frequent cystoscopic examination with fulguration when necessary (table 2). When first seen, 43 per cent, or nearly half of the patients, had experienced the symptoms of bladder tumor less than three months. Within one year of onset of symptoms, 69 per cent of the patients were under treatment. This figure coincides closely with the percentage of well-controlled patients, and, though it may be co-incidental, there is more reason to believe that a significant correlation exists.

Table 2 also shows that 22 per cent of the cases suffered some degree of hydronephrosis secondary to the bladder tumor, 5 per cent had pyelonephritis (unilateral or bilateral) and 1 per cent had rectovesical fistula. As a sidelight we determined that 33 per cent of the males, regardless of consideration as to age, had some degree of benign prostatic hyperplasia. This is slightly higher than most statistics reveal for men over 60.

PATHOLOGY

For several reasons, the pathological data are incomplete, and, at the same time, somewhat redundant as regards pathological classification of the tumors. In the first place, the followup includes cases back to 1942, at which time pathological diagnoses were far from uniform and clear cut. Secondly, Wesley Memorial Hospital has had several pathologists during that period of time. The present

TABLE 3. *Pathological types of bladder tumors*

	NONINVASIVE	INVASIVE	TOTAL
Transitional cell carcinoma	39 (30.7%)	22 (52.4%)	61
Transitional cell papilloma with malignant change	19 (14.9%)	2 (4.8%)	21
Transitional cell papilloma	16 (12.6%)	—	16
"Benign" papilloma	8 (6.3%)	—	8
Bladder polyps (? papilloma)	3 (2.3%)	—	3
Papilloma with malignant change	6 (4.9%)	9 (21.4%)	15
Carcinoma simplex	3 (2.3%)	3 (7.2%)	6
Adenocarcinoma	1 (1.0%)	—	1
Mucinous adenocarcinoma	2 (1.5%)	—	2
Undifferented carcinoma	3 (2.3%)	2 (4.7%)	5
Squamous cell			7

staff is very adept and accurate in their diagnoses, so that the tissues for the last seven years have been more accurately diagnosed. Finally, not in every case was a specimen sent for biopsy, though the clinical diagnosis was definite.

Table 3 illustrates the pathological types. Of 115 clinically diagnosed, noninvasive tumors, 105 were biopsied. Thirty per cent were diagnosed transitional cell carcinoma, 15 per cent transitional cell papilloma with malignant change, and 20 per cent fell into the benign papilloma group, including the transitional cell papillomas and bladder polyps. In the clinically invasive group of 41 cases, 38 were biopsied, and over 50 per cent proved to be transitional cell carcinoma and 21 per cent were papillomas with malignant change. Finally, there were seven cases of squamous cell carcinoma in our series. Of some interest, it is surprising that our three cases of adenocarcinoma were clinically noninvasive, and all are alive and well at this writing.

SURVIVAL TOTALS

Of the 180 cases included in our study, 18 were not included in the survival totals because of inadequate followup data. To all patients who had not been seen recently, either in the hospital or office, letters of inquiry were written. Eighteen persons failed to answer and are not, therefore, included.

Table 4 is a summary of the status of each patient at this writing without regard to length of time followed. Subsequent tables will discuss the length of survival. In table 4 we have divided the cases into three groups: 1) clinically noninvasive tumors as per the initial diagnostic impression; 2) clinically invasive tumors when first seen; 3) squamous cell tumors. Furthermore, because there is debate as to the validity of open suprapubic coagulation of bladder tumor, we divided the cases into two additional groups: –1) those treated by transurethral coagulation only, and 2) those controlled by suprapubic coagulation with or without subsequent transurethral coagulation. The criterion for the type of surgical approach was based on the size, location and accessibility of the tumor with consideration as to degree of invasiveness.

Table 4 shows that of 115 noninvasive tumors, 59 were treated by transurethral coagulation alone (from one to many times, depending upon the number

TABLE 4 *Survival totals*

	NO OF CASES	ALIVE & WELL	DEATHS	SEVERE RECURRENCE	SURVIVED STATUS?
Noninvasive (T U R)	59	74 0%	20 3%	—	—
Noninvasive (open surg)	56	60 7%	19 8%	5 3%	11 2%
Totals	115	68 8%	20%/6 9%	2 6%	8 6%
Invasive (T U R)	11	—	81 8%	18 2%	—
Invasive (open surg)	30	13 3%	70 0%	16 7%	—
Totals	41	9 7%	73 1%/48 3%	17 2%	—
Squamous cell (T U R)	1	—	100 0%	—	—
Squamous cell (open surg)	5	20 0%	60 0%	—	20 0%
Totals	6	16 7%	66 6%/66 6%	—	16 7%

Survivals—18 (letters written, not answered)

of recurrences) As of this writing, 74 per cent are alive and well and 20 per cent are dead Of the 56 cases treated by suprapubic cystotomy and coagulation, 61 per cent are alive and well, 20 per cent are dead, 11 per cent are alive but with questionable tumor status and 5 per cent are still having severe recurrences In summary, of the noninvasive tumors, nearly 70 per cent are alive and well and only 20 per cent are dead, but, of still greater importance, as per the second figure in the totals under the deaths column, only 6 9 per cent actually died of bladder tumor

Of interest is the fact that the patients with noninvasive tumor show approximately a 70 per cent alive and well survival regardless of the surgical approach It seems, therefore, that suprapubic cystotomy does not promote the spread of tumor and enables a more thorough eradication of the larger, less accessible neoplasms

Of the 41 cases of invasive bladder tumor, only 11 were treated solely by transurethral coagulation Of these, 82 per cent are dead and 18 per cent are having severe recurrences and 13 per cent are alive and well In summary, we see a discouraging picture for those patients diagnosed initially as having invasive bladder tumors Seventy three per cent are dead, nearly 50 per cent of the total having died from their tumor Seventeen per cent are alive with severe recurrences and only a scant 10 per cent are alive and well

Squamous cell tumors, of which we report 6 cases, are equally discouraging Only one was treated by resectoscopic coagulation, and he died of his tumor Of 5, managed by open surgery, 3 are dead, one is alive and of questionable status, and one is well The totals show that two-thirds died of their disease and only one patient survived with good health

SURVIVAL PERIODS

Of major interest to us in summarizing these case histories is a record of the overall survival period that is, the period of time from the date of the patient's

TABLE 5. *Survival period chart: Noninvasive tumors*

TOTALS		PERIOD OF OBSERVATION AFTER ONSET						
		0–6 mo.	6 mo.–1 yr.	1–2 yrs	2–3 yrs.	3–4 yrs.	4–5 yrs.	Over 5 yrs.
Alive & well	79	100%	—	50%	66.7%	78.6%	70%	77%
Deaths	23/8	—	100%/66.7%	33.3%/16.7	16.7%/0	0/0	30%/15%	12.5%/0
Severe recurrences	3	—	—	5.5%	8.6%	7.1%	—	—
Alive status?	10	—	—	11.0%	8.6%	143.%	—	10.5%
Total	115	1	3	18	12	14	19	48

KNOWN SURVIVAL: 115 PATIENTS. *ALIVE & WELL:* 68.7%. *DEATHS:* 20%. *OF CANCER:* 7.0%. *SEVERE RECURRENCES:* 2.6%. ALIVE-STATUS?: 8.7%.

TABLE 6. *Survival period chart: Invasive tumors*

TOTALS		PERIOD OF OBSERVATION AFTER ONSET						
		0–6 mo.	6 mo.–1 yr.	1–2 yrs	2–3 yrs.	3–4 yrs	4–5 yrs	Over 5 yrs.
Alive & well	4	—	—	—	—	25%	—	30%
Deaths	30/20	100%/100%	77.7%/22.2%	90%/63.6%	80%/60%	50%/50%	—	50%/40%
Severe recur	7	—	22.3%	9.1%	20%	25%	—	20%
Alive-status?	0	—	—	—	—	—	—	—
Totals:	41	2	9	11	5	4	0	10

KNOWN SURVIVALS: 41 PATIENTS. *ALIVE & WELL:* 9.7%. *DEATHS:* 73.3% *OF CANCER:* 18.8%. *SEVERE RECURRENCES:* 17.0%.

first bladder symptoms to the present time, with determination of their current health status.

As stated previously, all but 18 patients have been brought up to date in this study. They, or their relatives, failed to answer questionnaires as to their status. Tables 5 and 6 are constructed to illustrate the number of patients followed for each listed time interval and the percentages alive and well, dead, alive with severe recurrences, or alive and of questionable status in each time period. Further, of those dead, in each column the percentage who definitely died of their bladder tumor is listed to the right of the total per cent dead.

Table 5 includes the 115 cases of clinically noninvasive bladder tumors. Note that in the horizontal column marked total 48 cases lived over 5 years, 19 lived 4 to 5 years, 12 lived 3 to 4 years, 18 for 2 to 3 years, 3 survived only 6 months to 1 year, and 1 patient was followed from zero to 6 months.

Of the 48 patients who lived over 5 years, many of whom have been followed eight to ten years, 77 per cent are alive and well. Only 12.5 per cent are dead and the most remarkable observation is that *none* died of his bladder tumor. A scant 10 per cent are of unknown status, though alive. Of the nineteen who have been followed four to five years, 70 per cent are alive and well, 30 per cent are dead and 50 per cent of them died of their tumor, or 3 patients. Fourteen patients were observed three to four years and nearly 80 per cent of them are alive and well. Not one of this group of patients has died. A small fraction (7 per cent) are having severe recurrences and 14 per cent are of questionable status. Over 65 per cent of the 18 patients observed two to three years are alive and well, 33 per cent are dead—50 per cent of their bladder disease. Therefore, of the patients with initially noninvasive tumors followed more than two years, about 75 per cent are alive and well.

The 18 patients in this group seen from one to two years show only 50 per cent alive and well, 33 per cent are dead with half of these dead of tumor, and 11 per cent of questionable status. Five per cent are having severe recurrences.

Apparently, of the 3 patients followed 6 months to 1 year, two had pathologically invasive tumor, though clinically the tumors appeared noninvasive. These 2 patients died shortly after their first surgical procedure.

One patient who was recently seen at the time of this writing is alive and well.

The summary shown at the bottom of table 5 strikingly points out that only 7 per cent of 115 patients who lived from 6 months to well over 5 years, died of their tumor. Therefore, 93 per cent were effectively controlled and 68 per cent alive and well, as managed by either or both suprapubic and transurethral coagulation.

Table 6 includes an interval breakdown of the 41 patients diagnosed initially as having invasive bladder tumors. Ten lived over 5 years, and, of these, four died of their tumor, two are having severe recurrences and three are alive and well. Of four who were followed 3 to 4 years, two died of their tumor, one has severe recurrences and one is alive and well. Of the 27 patients observed up to 3 years, none are in good health. In the two to three year group, four out of five died and one is having severe recurrences. Of 11 who were followed one to two years, the largest single group in the invasive tumor category, 90 per cent are dead, 64 per cent of their tumor. Of 9 patients in the six months to one year group, 78 per cent are dead, but only 22 per cent definitely of cancer. Twenty-two per cent have severe recurrences. Finally, both patients followed less than 6 months died of tumor.

Table 6 is a discouraging reflection of the results in treating invasive tumor by coagulation. Of 41 patients, only 10 per cent are alive and well; whereas, 73 per cent are dead, 50 per cent of their cancer.

CONCLUSIONS

On initial cystoscopic or suprapubic examination of the bladder, the surgeon must determine to the best of his ability the degree of invasiveness of the tumor. His judgment should be re-inforced whenever possible by biopsy and pathological report of degree of invasiveness.

For those tumors placed in the noninvasive class, suprapubic resection and coagulation or transurethral coagulation alone, depending on size, location and type of tumor, provides adequate therapy with an excellent chance for a long survival.

There is no evidence of increased morbidity or spread of the cancer cells by the suprapubic approach and the advantages are numerous.

Uniformly poor results occur with invasive bladder tumors by the applied methods of conservative surgery and with those cases, which on initial examination show a moderate to high degree of invasiveness, the advisability of radical cystectomy early in the course of the disease, with diversion of the urinary stream to bowel or skin, should be seriously considered. It is possible that subsequent work with radioactive colloids may provide an additional means of treating invasive tumors but, as yet, this is in the experimental stage.

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LEIOMYOSARCOMA OF THE URINARY BLADDER: REPORT OF A CASE

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In 1949 we had the opportunity of treating a patient who had a leiomyosarcoma of the urinary bladder. This is an infrequently encountered lesion, but even more unusual is a survival for longer than one year. Of the 25 cases reported to date, only two have been alive without recurrences 1 year following treatment. Hager and Hunt's patient was "alive and well" 4 years after operation, and Lev and Bell reported a case in which they speculated, "the prognosis to be good for complete cure in this instance", although no follow-up was presented. The subject of the following case report is alive, well, and without recurrences some 3 years and 3 months following surgical excision of the tumor.

CASE REPORT

P. P. K., Register Number 16-266, a 21 year old Negro, was admitted to the Thayer Veterans Administration Hospital on February 4, 1949 complaining of "bleeding when I pass my water."

Three weeks prior to hospitalization he suffered the insidious onset of dysuria, frequency, urgency, and bilateral costovertebral angle pain of a dull and constant nature. He was seen at that time by his family physician who prescribed sulfadiazine. The symptoms persisted despite this therapy, and one week later he began to urinate gross blood for the first time in his life. The bleeding occurred throughout the act of micturition and clots were passed painfully from time to time. He denied having fever, chills, weight loss, suprapubic pain, increased fatigue, or a urethral discharge during the present illness.

Pertinent past history revelations were that in 1947 he was successfully treated for gonococcal urethritis by penicillin, and that he had had recurrent episodes similar to the present illness since 1947, but never previously complicated by hematuria. Because of the unrelenting hematuria he sought hospitalization.

On admission to the hospital his blood pressure was 120/70, pulse 80, respirations 20, temperature 98.6F. He was a healthy appearing, young Negro in no distress. The mucous membranes of the oral cavity were unusually pale. The lungs were normal. The heart was normal except for a soft systolic murmur at the base. The abdomen was scaphoid, somewhat tense, but without tenderness. There were no palpable abdominal organs or masses. Mild tenderness was present in both costovertebral angles. The genitalia were normal. The prostate was boggy, somewhat tender, and moderately enlarged. There were no palpable rectal masses and no blood. The remainder of the physical examination was within normal limits. No urethral secretion was obtained by massage. Observation of the patient voiding confirmed the history of gross hematuria throughout the act.

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The results of the laboratory tests were as follows: hemoglobin 7.5 gm.; red blood count 3,500,000; white blood count 11,250; differential white count, normal; sickle cell preparation negative for sickling at 24 hours. Urinalysis: reaction, acid; specific gravity 1020; albumin 4 plus; sugar, negative. Microscopic: gross blood; no casts. Staphylococcus aureus was cultured from the urine. The phenolsulfonphthalein excretion was 45 per cent in 15 minutes; nonprotein nitrogen was 25.9 mg. per cent; sulfadiazine blood level, 0 mg. per cent; Kahn, negative. The chest x-ray was normal. An excretory urogram was normal. Cystogram revealed some slight flattening of the anterior aspect of the bladder. Cystoscopic examination was carried out on February 11, 1949, under local anesthesia. An elevated, irregular, ulcerated tumor, approximately 2 cm. in diameter was found to involve the anterior bladder wall. The tumor was biopsied, but on microscopic section neoplastic cells could not be found, rather only those inflammatory changes of cystitis. Subsequently on February 16, 1949, the cystoscopic examination was repeated under spinal anesthesia. The findings were unchanged, though some gross edema had developed in the interim about the site of the previous biopsy. What was thought to be a more adequate biopsy was taken at this time and the area fulgurated. Once more the microscopic sections contained only inflammatory changes and no evidence of tumor. Following cystoscopy, a bimanual examination under spinal anesthesia revealed a spherical mass calculated to be about the size of an English walnut, which was freely movable and thought to be within the wall of the bladder. The cystograms were repeated, and this time more clearly demonstrated the defect in the anterosuperior wall of the bladder (fig. 1). During this period of diagnostic procedures, the anemia was corrected by whole blood transfusions despite continuation of the bleeding, and the urine became sterile on penicillin therapy.

On March 7, 1949, under spinal anesthesia, a midline suprapubic approach was employed to explore the bladder. On gaining the prevesical space, an egg-sized, circumscribed mass was found to be presenting anteriorly from its incor-

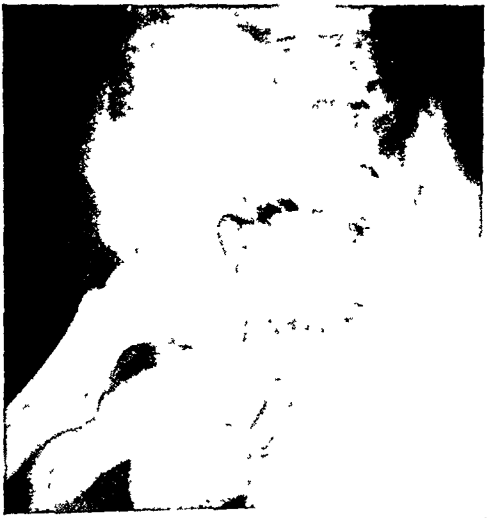

FIG. 1. Defect in anterior bladder wall as demonstrated by cystogram

poration within the anterior bladder wall. An attempt to dissect the peritoneal reflection off the tumor and bladder was fraught with the possibility of entering the tumor due to the firm adherence of the peritoneal reflection to the tumor, and was, therefore, abandoned. Consequently, the peritoneum was incised in such a manner that that portion of peritoneum attached to the tumor was undisturbed. The resultant peritoneal defect was closed transversely with a continuous catgut suture. The tumor with the attached islet of peritoneum was then excised from the bladder by dividing all layers of the bladder with the circumscribing incision. Frozen sections showed the tumor to be a sarcoma. It was felt that removal of more tissue about the periphery of the defect might improve the prognosis; therefore, a 2 cm. cuff of normal appearing bladder wall was excised circumferentially about the defect. The remaining bladder did appear quite small, but closure of the cystotomy wound about a Malecot catheter did not appreciably alter the trigonal structures. The abdominal wound was then closed in the usual manner, after placing a rubber tissue drain in the prevesical space.

Grossly the specimen consisted of a firm, ovoid tumor mass, 6 by 4 by 3.5 cm. in size, well contained within the surrounding fascia and fibrous tissue and on one surface covered by bladder mucosa. The cut section was composed of pale gray, fleshy tissue with rather large areas of yellowish necrosis (fig. 2).

Microscopically the tumor was fairly well circumscribed, but active invasion of the bladder muscle was evident in several sections (fig. 3). The tumor was composed of interlacing bundles of spindle cells with plump oval or elongated nuclei and rather abundant cytoplasm (fig. 4, *A*). The cells composing the tumor stained selectively for smooth muscle by Masson's trichrome method. The more peripheral areas were compactly cellular and occasional mitotic figures were seen (fig. 4, *B*). In the more central portions the cell bundles were edematous and large areas of necrosis were present. The blood supply of the tumor was by endothelial lined sinusoids, surrounded closely by neoplastic cells.

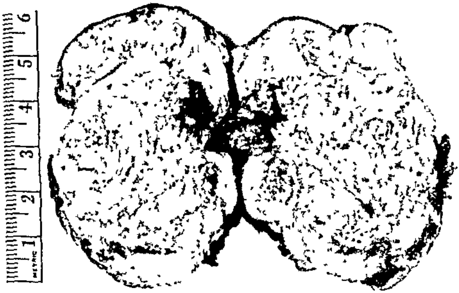

FIG. 2. Cut section of tumor at its greatest diameter. Section consists of whorls of fleshy gray tissue with large areas of yellowish necrosis.

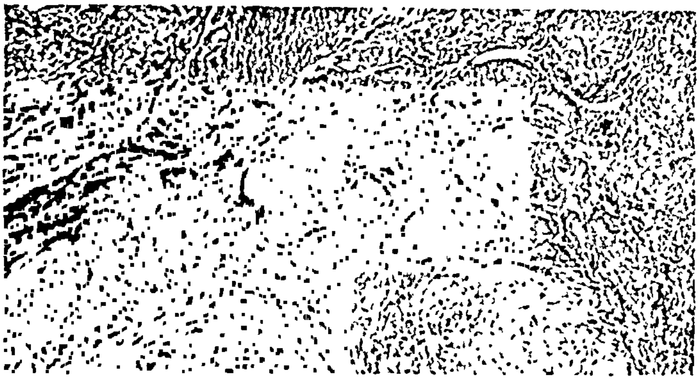

FIG. 3. Upper portion of section represents pre-existing bladder musculature with peninsula extending downward which is surrounded and invaded by tumor. Portion of tumor on right is edematous.

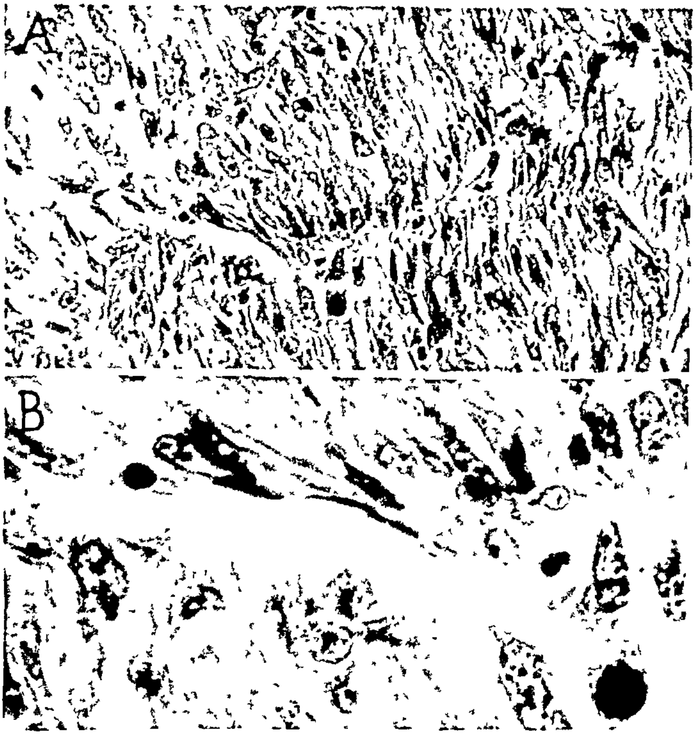

FIG. 4. *A*, field chosen from actively growing peripheral area to illustrate rather dense cellularity of tumor and endothelial lined blood sinusoids supplying tumor Mitotic figure is present in center of field. *B*, higher power of mitotic figure shown in *A*.

The postoperative course was uneventful except for the culture of B. cloacae from the urine. This infection subsided on sulfasuccidine treatment. The suprapubic wound had closed by the fourteenth postoperative day and he was voiding without difficulty. The bladder capacity one month postoperatively was 8 ounces, as determined by the maximum amount of urine the patient could retain without undue distress. When the patient returned for the first follow-up visit 4 months postoperatively, he was complaining of a urethral discharge and dysuria, but no more bleeding. A smear of the discharge disclosed gram negative intracellular diplococci. The gonococcal infection was cured by penicillin and sulfadiazine. Later, cystoscopy revealed no evidence of recurrence of the tumor and the bladder was considered normal.

Subsequently, this patient has been followed at six month intervals, with no evidence of recurrence of the tumor.*

DISCUSSION

Due primarily to the compilation of cases of leiomyosarcoma by Kretschmer and Doerhing, and Crane and Trembly, together with case reports by Lev and Bell, Mackles, et al., and Fister and Lund, some of the characteristics of this unusual tumor have come to light. The signs and symptoms do not deviate from those of the more common bladder neoplasms, hematuria being the cardinal sign. The tumor occurs in the male three times more frequently than in the female. It has been seen to arise from all parts of the bladder wall, but usually at some distance from the trigone, and none has been reported as being primary in the trigone. If one discounts the case of Mackles, et al., in which there was not only sarcoma but also a papillary carcinoma, there are only 2 cases in the series in which distant metastases were demonstrated.

Unfortunately, these tumors may grow outwardly and peripherally for a considerable time before invading the mucosa and causing hematuria, or they may produce hematuria at an earlier date, as in our case. Therefore, the time from the onset of hematuria to treatment is not a reliable criterion of the duration of growth of the tumor. Certainly, the sooner definitive treatment is instituted following the onset of symptoms the more favorable will be the prognosis.

The fact that this tumor rarely metastasizes should make it one of those most amenable to local radical excision and the overall results should be improved. Wide local removal is, therefore, the treatment of choice, whether it requires only a segmental cystectomy, a total cystectomy, or a radical pelvic evisceration. Today, with the newer operative techniques and supportive measures, we should be able to lengthen the survival time of patients with this type of malignancy, and possibly, and we say this with some trepidation, obtain a cure.

SUMMARY

A case of leiomyosarcoma of the urinary bladder is reported. The patient is alive, well, and without recurrence 3 years and 3 months following surgical excision.

Some of the characteristics of this rare bladder neoplasm are discussed, and it is speculated that the survival time should be improved with local radical surgical excision.

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* The patient moved to Camden, Ohio, in September 1951, and we are indebted to Dr. Dale T. Mullins and the Urology Staff of the Cleveland Veterans Administration Hospital for the more recent follow up examinations.

ADDITIONAL DATA

We have received a report from Dr. A. P. Rhamy of Crile V. A. Hospital, Cleveland, Ohio, dated March 25, 1954, stating that a cystoscopic examination on that date revealed no recurrence of the tumor.

H. S. S.

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MUCINOUS ADENOCARCINOMA IN A URACHAL CYST PRODUCING PSEUDOMYXOMA PERITONAEI

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Pseudomyxoma peritonaei was first reported by Wells[1] in 1865 when he described two cases of myxomatous degeneration of the peritoneum associated with mucinous cysts of the ovary. For over three decades this condition of "mucous ascites" was only seen in cases in which an ovarian lesion with mucoid elements was present In 1901, Frankel[2] reported a case in which a ruptured mucocele was found in the appendix of a man. Since then, pseudomyxoma peritonaei has been described as occurring secondary to mucinous adenocarcinoma of the gallbladder, of a caecal diverticulum or of a remnant of the omphalomesenteric duct[3] In the majority of cases, however, it is associated with a low grade pseudomucinous cystadenocarcinoma of the ovary, and in most of the remaining cases it is associated with a similar lesion of the appendix

Hayes and Segal[4] reviewed the literature on this subject in 1945 and established the fact that tumors arising in a urachal remnant are usually adenocarcinomas and that the majority of these are of the mucinous type Begg[5] has satisfactorily accounted for this from the histologic standpoint by demonstrating that the urachus represents a division of the original cloaca, and its cuboidal epithelium has retained the potential for producing mucin. Loeb,[6] Hurwitz, Jacobson and Ottenstein,[7] and other authors have reported cases in which a mucinous adenocarcinoma arose in the urachus and invaded the bladder In a cursory review of the literature, we were unable to find a report of a case in which pseudomyxoma peritonaei was associated with a urachal cyst The following case represents such an occurrence

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* Now practicing in Phoenix, Arizona

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REPORT OF CASE

A salesman, aged 65 years, came to the Mayo Clinic on July 31, 1951, because of a dull, continuous ache which had been present in the left lower quadrant of the abdomen for 6 weeks and had increased gradually in severity. The dull ache had been accentuated slightly by constipation, coughing or long automobile rides. Defecation or assuming the supine position had afforded some relief. The ache was not associated with nausea, diarrhea or other gastro-intestinal symptoms. The patient had lost 10 pounds (4.5 kg.) in the preceding year.

Nocturia had been present for 4 or 5 years, and the patient had had to micturate once or twice each night. Dribbling of urine occasionally had occurred after micturition. The patient had had an attack of appendicitis in January 1950, and appendectomy had been performed at that time.

Physical examination revealed moderate tenderness to the left of the umbilicus and prostatic hypertrophy, grade 2 (on the basis of 1 to 4). The enlarged prostate gland felt benign. Rectal examination disclosed small, external and internal hemorrhoids. The results of laboratory tests were normal. Roentgenologic examination of the thorax, colon and lumbar segment of the vertebral column did not reveal any abnormality. Excretory urography did not reveal any apparent abnormality of the urinary tract, but it did disclose a shadow caused by calcification and situated just above the vesical area (fig. 1). This was considered suggestive of calcification within an intra-abdominal cyst.

Because the symptoms subsided almost entirely, the patient was permitted to return to his home on August 8, 1951. An anticonstipation diet was prescribed, and the patient was advised to return to the clinic if his symptoms persisted.

The patient returned to the clinic on May 8, 1952. The dull, aching pain had shifted to the suprapubic area, and had increased in severity. It had been associated with a bearing down sensation. The signs and symptoms of urinary obstruction had become more pronounced, and the patient had noted an interruption of his urinary stream.

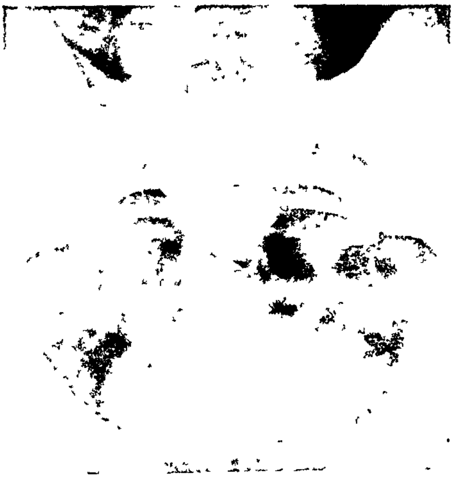

FIG. 1. Crescentic shadow of calcification above vesical area

The results of physical examination were the same as they had been at the time of the previous examination. The results of laboratory tests and roentgenologic examination were normal. The bladder contained 10 cc. residual urine. Cystoscopy disclosed enlargement of both lateral lobes of the prostate gland which appeared to be causing urinary obstruction.

On May 5, 1952, 32 gm. of prostatic tissue was removed by means of transurethral resection. Pathologic examination of the excised tissue revealed adenofibromatous hyperplasia. The suprapubic pain disappeared after the operation. When the patient was dismissed on June 11, 1952, he mentioned that the dull ache in the left lower quadrant of the abdomen had returned. This ache apparently had been overshadowed by the suprapubic discomfort prior to the operation.

The patient again returned to the clinic on December 11, 1952. The pain in the left lower quadrant of the abdomen had increased in severity, and the patient had been able to obtain relief only by lying in the prone position. He had lost 5 pounds (2.3 kg.) since his last visit to the clinic.

Physical examination revealed that the tenderness still persisted in the left lower quadrant of the abdomen. Palpation did not disclose any abdominal mass. Laboratory tests did not reveal any abnormality, but roentgenologic examination of the stomach disclosed a small diaphragmatic hernia. Roentgenographic examination of the abdomen did not reveal any change in the crescentic shadow which was noted at the time of the patient's first visit to the clinic.

An exploratory laparotomy was performed on December 15, 1952. Mucinous material was present throughout the peritoneal cavity. Microscopic examination of this material disclosed a mucinous adenocarcinoma, grade 1. A calcified mass, which measured 4 by 3 cm., was situated on the anterior abdominal wall near the dome of the bladder. The mass, which apparently was a cyst of the urachus, was removed (fig. 2). The pathologist reported that the surgical specimen con-

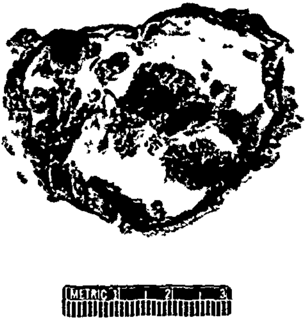

FIG. 2. Adenocarcinoma of urachal cyst. Wall of cyst is thickened, and cyst contains mucus.

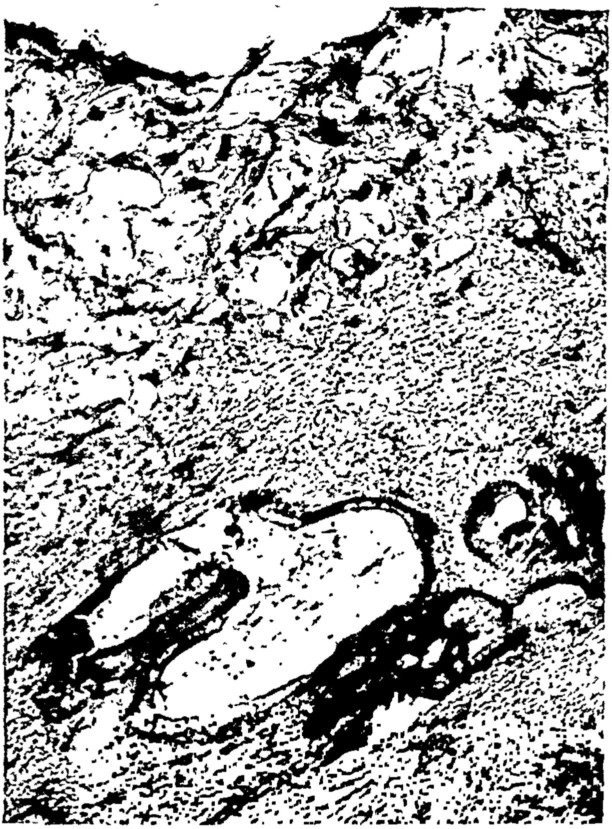

FIG. 3. Mucinous adenocarcinoma of urachal cyst (hematoxylin and eosin stain; X 42).

sisted of a multilocular, encapsulated, calcified mass, which was 4 cm. in diameter and contained a mucinous adenocarcinoma, grade 1 (fig. 3).

In order to exclude the appendix which had been removed elsewhere as the primary source of the mucinous adenocarcinoma, multiple sections of this organ were examined through the courtesy of Dr. R. E. Weland (Cedar Rapids, Iowa). There was no evidence of a mucocele or neoplasm being present.

His postoperative course was uneventful and he was dismissed from the hospital on December 27, 1952, and returned home on December 30, 1952. Arrangements were made for the patient to receive roentgen therapy to the entire abdomen. He was to return to the clinic in three months, at which time the advisability of intraperitoneal administration of radioactive colloidal gold was to be considered.

COMMENT

The surgical finding of mucus scattered throughout the peritoneal cavity and the histologic finding of slowly growing adenocarcinoma producing this mucus are the features which are necessary for a diagnosis of pseudomyxoma peritonaei. Such a combination of circumstances was found in the case which we have reported. It is not sufficient merely to have mucus in the peritoneal cavity because it is possible for a benign cyst which contains mucus to rupture and spill the mucoid material throughout the peritoneal cavity. This will be absorbed unless there is an associated implantation of glandular tissue from carcinoma cells which continues to produce more mucus. In most cases of pseudomyxoma peritonaei the primary source of the mucoid material has been a mucinous cystadenocarcinoma of the ovary. Less commonly, a malignant mucocele of the appendix has been the source of the material. An occasional case has been reported in which a retroperitoneal cystadenocarcinoma beginning in a cyst has been the primary source.

SUMMARY

This report is based on a case in which a mucinous adenocarcinoma developed in a calcified urachal cyst and extended intraperitoneally to produce pseudomyxoma peritonaei. The necessity of ruling out a urachal cyst as the site of origin of pseudomyxoma peritonaei is worthy of mention.

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PROLAPSE OF THE URETHRA IN YOUNG GIRLS

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Moffett and Banks[1] recently reported 4 cases of prolapse of the urethra in Negro girls between the ages of three and seven. They stressed the relative rarity of this condition in young girls as other authors[2, 3, 4] have done, and suggested a simple form of treatment. Within a period of 8 months we have seen and treated four young girls for a protrusion of the urethra through the meatus. The fifth case included in this series was a private patient of a member of our staff. All the patients were young, well nourished and well developed Negro girls. The youngest was 3 years of age and the oldest was eight. The purpose of this publication is to report these 5 cases of prolapse of the urethra in young girls and to re-affirm the effectiveness of simple complete circular amputation with a cautery loop in the treatment of this disease.

REPORT OF CASES

Case 1. D. L., a 3 year old Negro girl, was brought into the hospital by her mother because she noticed that the child was "bleeding from her privates." The mother reported that during the previous 12 months the child had many upper respiratory infections which were usually associated with frequent bouts of severe coughing. The mother particularly noted that it was during a coughing spell that she saw blood "running" from the genitalia for the first time. There were no associated urinary symptoms. Physical examination revealed an injected pharynx with a mucopurulent discharge from both nostrils. Examination of the vaginal introitus demonstrated a dark red edematous circular prolapse of the urethral mucosa which measured approximately 1.5 cm. in diameter and protruded about 0.5 cm. The mass was tender and bled easily when touched. After the upper respiratory infection had subsided, laboratory studies including a catheterized urine specimen, complete blood counts, Kahn test, excretory urogram and observation cystoscopy were completed and were found to be normal. The urethral lesion was first treated with hot sitz baths, and on the fifth day the entire prolapse was excised without any difficulty by the cautery loop. No approximating sutures were used. Bleeding was insignificant. The patient was allowed out of bed the evening of surgery and was discharged on the fourth postoperative day. She was last seen two months after the operation. Urinary symptoms and evidence of stricture formation were absent.

Case 2. B. J. G., a 4 year old Negro girl, was admitted to the hospital because

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of bleeding from the vagina. Her mother related that the child had had one episode of similar bleeding four months previously. This subsided spontaneously without any treatment. At no time were there any urinary symptoms. Examination revealed an edematous, inflamed prolapsed urethral meatus measuring approximately 1 cm. in diameter. At the most dependent portion of the prolapse was a small ulcerated area. A catheterized urine specimen, Kahn test, observation cystoscopy and excretory urogram were normal. The patient was treated with hot sitz baths for 5 days and then the prolapsed urethral mucosa was removed flush with its base with the cautery loop. Bleeding was minimal. The patient made an uneventful recovery and was discharged on the fifth postoperative day. She was last examined 3 months following the operation and had no stricture of the urethral meatus.

Case 3. J. A. S., an 8 year old Negro girl, was admitted to the hospital complaining chiefly of burning on urination of 5 days' duration. Her mother also stated that the child had a "swelling in the vagina" which she first noticed 3 years earlier following a criminal attack. The swelling apparently had not increased in size during this interval. There were no other complaints. Examination revealed a noninflamed prolapse of the urethra. The mass measured 1 cm. in diameter and protruded approximately 0.4 cm. A catheterized urine specimen, blood counts, Kahn test and excretory urogram were all normal. Observation cystoscopy demonstrated mild trigonitis and urethritis. The lesion was first treated with hot sitz baths and on the third day, the prolapsed mucosal cuff was removed with the cautery loop. A slight amount of bleeding occurred on the day of the operation but this cleared spontaneously at the end of the 12 hours and catheterization was not necessary. The patient was discharged on the fourth postoperative day. She was examined 2 months after the operation and had no urinary difficulties or any evidence of stricture formation. A No. 18 infant sound was easily passed into the bladder. Figure 1 shows the preoperative and postoperative photographs.

Case 4. B. B., a 3 year old Negro girl, was admitted to the hospital because her mother had noticed during the previous 2 days "spots of blood" on her under-

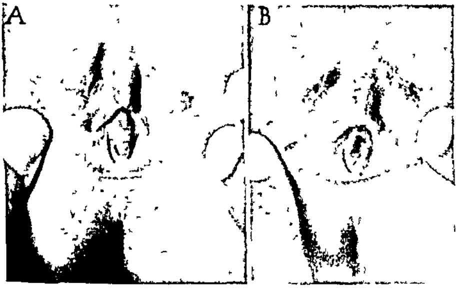

FIG. 1. Case 3. *A*, preoperative photograph showing mass protruding from urethra. *B*, urethral meatus 2 weeks postoperative. Area has completely healed.

clothes. Urinary symptoms or other complaints were absent. Examination revealed a dark, purplish-red mass protruding from the urethral meatus and almost completely filling the vaginal introitus. The mass was tender to touch and bled easily. A catheterized urine specimen, blood counts, Kahn test, excretory urogram and observation cystoscopy were all normal. The patient was first treated with hot sitz baths and on the third day, excision of the prolapsed mucosa was done with the cautery loop. No urinary symptoms developed and the child was discharged on the sixth day after surgery. On her last visit to the clinic, two months postoperatively, no stricture formation was noted. A No. 16 infant sound was easily passed into the bladder.

Case 5. *B. L., a 3 year old Negro girl, was admitted to the hospital with a history of bleeding from the vagina of 7 days' duration. She had no urinary complaints. The mother related that the child had sustained a hard fall on the floor 2 weeks previously. Nothing abnormal was noted at that time. Examination in the hospital revealed a prolapse of the entire circumference of the urethral mucosa through the meatus. The entire mass was acutely inflamed and completely obscured the meatal orifice. A splinter of wood was noted in the exposed mucosa and removed. The remainder of the physical examination was normal. A catheterized urine specimen, blood counts, Kahn test, observation cystoscopy and excretory urogram were normal. She was treated with hot sitz baths for 6 days and then the entire prolapsed mucosal cuff was removed with the cautery loop. No bleeding occurred. The patient was discharged on the third postoperative day. Her physician reported no stricture formation on the last examination which was made 4 months postoperatively.

Many predisposing and precipitating factors have been listed in the literature to explain prolapse of the urethra. In three of our cases a probable cause could be elicited. Strain from severe bouts of coughing was present in case 1: it was during a coughing spell that the mother first noted blood. Rape has been listed by Berry and Greene[4] as an infrequent cause of prolapse. In case 3, the mother first noted the swelling in the vagina soon after the patient was criminally attacked. Trauma was present in case 5; the finding of a splinter of wood embedded within the prolapsed mucosa supported this belief. No apparent etiological factor could be elicited in cases 2 and 4. It was apparent from the reports in the literature that many factors may produce prolapse of the urethra. Young girls having congenitally poor tissue structure locally or an abnormal mucosal redundancy are probably more susceptible to the development of prolapse of the urethra when they are exposed to such stress or straining factors as severe coughing, constipation or trauma.

The usual clinical findings have been urethral bleeding and the presence of a mass in the vaginal introitus. Urinary symptoms have been infrequent; when present, they were mild. In all our patients catheterized urine specimens and excretory urograms were done and found to be normal. In only one case was mild trigonitis noted on observation cystoscopy. The prolapsed mucosa surrounded the entire circumference of the meatus in all our cases.

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* A private patient of Dr. Merle Herriford who kindly allowed us to include this case in our report.

Many methods are available for the treatment of prolapse of the urethra Our procedure has been similar to that suggested by Moffett and Banks[1] Preoperative hot sitz baths are given for 3 to 5 days This helps in reducing some of the inflammation and aids in establishing a line of demarcation between the normal urethral mucosa and the inflamed prolapsed mucosa The surgical technique in removing the prolapse is simple The prolapse is put under slight tension by grasping anteriorly and posteriorly with two Allis forceps The cautery loop then quickly and completely removes the entire prolapsed urethra flush with its base at the line of demarcation No sutures are used to approximate the cut edges In none of our cases has it been necessary to use a catheter to control bleeding Little to no discomfort has occurred during the postoperative period On the day of discharge the urethra was dilated with infant sounds In the 3 and 4 year old patients a No 16 sound was used In the 8 year old girl a No 18 sound was used This was repeated weekly for two visits in the out patient clinic and then monthly for two or three visits In none of our cases did strictures develop

SUMMARY

Five cases of prolapse of the urethra in young girls are reported Complete circular amputation of the prolapsed mucosa with the cautery loop was found to be an effective and simple method of treatment The postoperative course of all our patients was surprisingly free of urinary symptoms There has been no evidence of postoperative stricture formation with this method of treatment

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TUBERCULOUS ULCER OF THE PENIS: PRIMARY SURGICAL EXCISION

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Penile tuberculosis is rare. In a recent complete review of the literature Lewis[1] found only 110 cases reported. Of these, 72 were the result of ritual circumcision in Jewish infants. Tuberculous affections of the penis have become singularly rare since the widespread adoption of surgical principles in circumcision. Aside from penile tuberculosis resulting from circumcision, Lewis found that the lesion was acquired either primarily as a result of coitus, fellatio or the wearing of infected clothing; or secondarily from tuberculous foci elsewhere in the body. The majority of the latter group were associated with urinary tract or seminal tract tuberculosis; only three cases having been reported in which the penis was involved following pulmonary tuberculosis without evidence of genito-urinary disease. The following case is reported because of successful surgical treatment of this rare condition.

W. T. (WGH 30196), a 38 year old white married machinist, entered the hospital on January 1, 1952 complaining of an ulcerated lesion on the shaft of the penis, which had begun 3 weeks earlier as a nontender superficial nodule. He could not recall any trauma or relation of the onset of the lesion to coitus. After incision by a local physician on the supposition that it was an abscess, the lesion rapidly ulcerated and enlarged.

The patient gave a history of hospitalization for 9 months in 1945 for pulmonary tuberculosis. Subsequent chest surveys, the last in October 1951, had revealed no evidence of activity. He denied cough, weight loss, fever, urinary symptoms or other systemic manifestations. His wife did not have tuberculosis and he denied extramarital sexual contact. There was no past history of venereal disease.

Examination revealed a healthy appearing, stocky young man. On the right side of the shaft of the penis there was a large ulcer measuring 4 by 4 cm. with raised undermined edges and a necrotic base covered with purulent exudate (fig. 1, *A*). The affected area was not painful or tender, and no inguinal adenopathy was present. The prostate, seminal vesicles and scrotal contents were normal to palpation and the prostatic fluid was of normal microscopic appearance. Blood count, sedimentation rate and urinalysis were normal. Chest films revealed minimal fibrosis in the right mid and lower lung fields, but were otherwise indeterminate. Excretory urogram showed normal upper tracts. Urine examinations were negative for acid fast bacilli on concentrated direct smear, culture and guinea pig inoculation. Extensive bacteriological studies were done without disclosing specific micro-organisms. Biopsy of the ulcer margin revealed a granulomatous lesion with no acid fast bacilli or spirochetes seen on special stains.

Accepted for publication February 27, 1953.

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[1] Lewis, E. L.: Tuberculosis of the penis: A report of 5 new cases and a complete review of the literature, J. Urol., 56: 737, 1946.

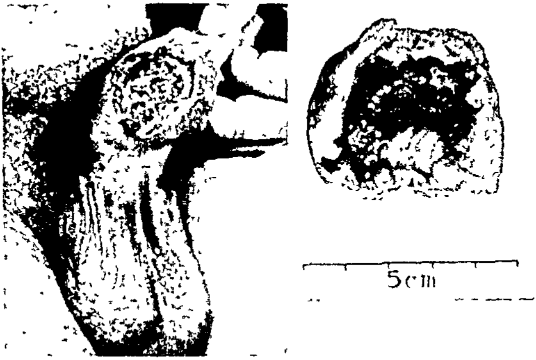

Fig. 1. Tuberculous ulcer of penis. *A*, at time of admission. *B*, surgical specimen following preoperative preparation.

The patient was treated on the dermatology service with sulfadiazine and chloramphenicol orally and with neomycin ointment locally. Following 7 weeks of this regimen the ulcer base became clean and presented healthy granulations, although the edges remained indurated and undermined. He was transferred to the urology service with a diagnosis of nonspecific granulomatous ulcer of the penis. Following additional local treatment with potassium permanganate soaks. the edges of the ulcer softened.

Because of the large defect present, surgical extirpation and plastic reconstruction were deemed advisable. The preoperative diagnosis was nonspecific granulomatous ulcer of the penis. The ulcer was excised with a 5 mm. skin margin between transverse elliptical incisions down to Buck's fascia (fig. 1, *B*). The ulcer base was moderately adherent but did not extend deep to Buck's fascia. For-

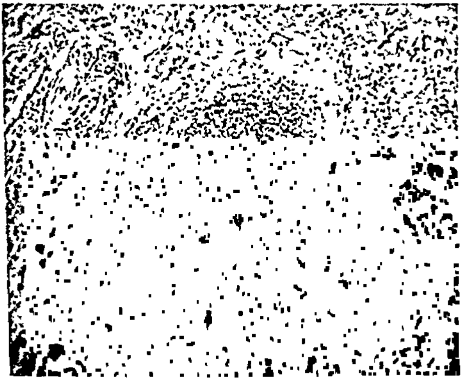

Fig. 2. Characteristic tuberculoid appearance. Acid-fast bacilli were found in Ziehl-Nielsen preparation.

tunately, the patient was not circumcised and therefore closure of the defect was readily achieved by retracting the prepuce, providing sufficient skin to slide over the shaft of the penis.

Microscopic examination revealed a tuberculoid granulatous base with numerous tubercle formations, giant cells and round cell infiltration. Acid fast bacilli were identified in the Ziehl-Nielsen preparation after intensive search (fig. 2).

Following the report of the tuberculous nature of the lesion, he was given streptomycin 1 gm. twice weekly and paraminosalicylic acid 12 gm. daily. The wound healed per primam, but the paraphimosis caused by the type of closure required a small dosal slit which corrected the constriction and edema. One month postoperatively the wound was entirely healed, and edema had abated (fig. 3). The patient was continued on streptomycin and paraminosalicylic acid therapy for 6 months, and the wound remained healed.

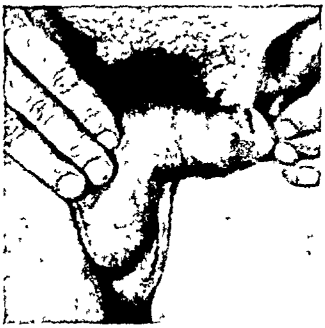

FIG. 3. Appearance of wound 6 months postoperatively

The patient has now been followed for 22 months since surgery and has remained well without recurrence of local or systemic tuberculosis.

DISCUSSION

The etiology of this tuberculous ulcer remains obscure. Studies were done on the patient's wife and no evidence of pulmonary or genital tuberculosis was found. Several possibilities exist as to its origin: that it resulted from contact with a partner having pelvic or pulmonary tuberculosis and was acquired in the act of coitus or fellatio; that it occurred as a result of re-inoculation by contact with his own infected sperm, urine or sputum in the vagina of his partner; or that it represents secondary hematogenous spread from his known but alleged inactive pulmonary disease or from his undisclosed genito-urinary tuberculosis.

The diagnosis in this case depended upon the finding of acid fast bacilli in the second surgical specimen referred for microscopic examination. However, the gamut of bacteriological investigations was helpful in ruling out other more common lesions of the penis.

Lewis states that the treatment of tuberculosis of the penis has been most unsatisfactory; that heat, ultraviolet, radiotherapy, chemicals and surgical excision have all been unsatisfactory by and large, and that generally the prognosis is quite poor. However, since the advent of recent tuberculostatic agents, the outlook has undoubtedly been altered. Excisional surgery and cure are now feasible in pulmonary, renal and seminal tract tuberculosis since miliary spread and local recurrence can be well controlled with streptomycin, paraminosalicylic acid and more recently, isoniazid drugs. It is therefore to be expected that similar treatment aimed at surgical cure will afford good results in large cutaneous tuberculous ulcers, and may indeed be the treatment of choice.

SUMMARY

A case of tuberculous ulcer of the penis is presented. The disease, although rare, has been recalcitrant in past reported cases. Successful surgical management of the case consisted in wide excision of the ulcer, plastic closure and maintenance of the patient with streptomycin and paraminosalicylic acid postoperatively. It is suggested that this may be the treatment of choice in tuberculous ulcers of the penis or of the skin elsewhere.

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IDIOPATHIC HEMORRHAGIC INFARCTION OF THE TESTICLE IN THE NEWBORN

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Hemorrhagic infarct of the testicle in the newborn infant is rarely recognized, and orchiectomy in the neonatal period is a rare surgical indication. This condition as seen in the first and second decades of life, however, is not uncommon and is most often the result of torsion of the spermatic cord. Testicular infarction has been reported as a complication of strangulated hernia in the infant[1] and has been noted as a result of torsion of the spermatic cord in the newborn.[2, 3, 4] However, the presence of hemorrhagic infarct of the testicle in the newborn has been observed in the absence of demonstrable evidence of torsion of the spermatic cord, hernia or trauma incident to labor. That this condition of complete gangrene of the testicle in the newborn can be a spontaneous development without predisposing factors or an antecedent exciting cause remains very questionable.

Five cases of hemorrhagic infarction of the testicle in the newborn due to torsion of the cord have been reported, and four cases of testicular infarct in the newborn, one by Campbell,[5] two by MacLean[6] and one by Ravich[7] with no demonstrable cause have been described. The fifth case of idiopathic hemorrhagic infarct of the testicle in the newborn is herewith presented.

The purpose of this paper is to specify the diagnostic criteria of infarct of the testicle in the newborn infant that have been thus far recognized in the relatively few cases which have been cited. This disease entity is apparently far more common than medical literature would indicate in view of the numerous instances of unexplained unilateral atrophy of the testicle as encountered in the adult. It is probable that the obstetrician, pediatrician and general practitioner in the past have encountered this condition which represented an obscure, benign, incomprehensible affection of the hemiscrotum which followed an uneventful course during the unknown process of aseptic testicular gangrene and atrophy.

CASE REPORT

Baby J. T. (No. 52-87), birth weight 7 pounds 7 ounces, was born at the Lutheran Memorial Hospital on January 27, 1952 of a 24 year old primipera

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Read before the annual meeting of the Medical Society of the State of New Jersey, Atlantic City, N. J., May 17, 1953.

[1] Rosenblatt, M. S. and Bueermann, W. H.: Strangulated hernia with acute hemorrhagic infarction of testicle in infants. Northwest Med., **38**: 18, 1939.

[2] Biorn, C. L. and Davis, J. H.: Torsion of the spermatic cord in the newborn. J.A.M.A., **145**: 1236–1238, 1951.

[3] Campbell, M. F.: Torsion of the spermatic cord in the newborn infant. J. Pediat., **33**: 323–327, 1948.

[4] Taylor, M. R.: A case of testicle strangulated at birth: Castration; recovery. Brit. Med. J. **1**: 458, 1897.

[5] Campbell, M. F.: Hemorrhagic infarction of the testicle in newborn. Pediatric Urology. New York: Macmillan Co., 1936, p. 113.

[6] MacLean, J. T.: Hemorrhagic infarct of the testicle in the newborn. Surg., Gynec. & Obst., **76**: 319, 1943.

[7] Ravich, R. A.: Hemorrhagic infarction of the testicle in the newborn. J. Urol., **57**: 875, 1947.

following normal labor, vertex presentation and spontaneous delivery. The mother who is a registered nurse examined the newborn infant within two hours after delivery and observed an enlargement of the left scrotum which was discolored and which did not arouse the infant on palpation.

Examination disclosed a smooth, nontender, globular, firm mass the size of a large green olive occupying the left scrotum, the wall of which was of bluish discoloration and nonedematous. The scrotal wall was adherent to the mass which was not in an elevated position in the scrotal sac. There was ample distance for palpation of the spermatic cord between the superior border of the mass and the external inguinal ring which was not dilated. There was nothing significant upon palpation of the left spermatic cord. The left scrotum did not transilluminate light. The right scrotal sac showed evidence of a small amount of hydrocele fluid. The right testicle was of normal size. A provisional diagnosis of left hematocele and right hydrocele was made.

On the fifth day of life incision and drainage of the apparent hematocele were decided upon since there was no change in the size or consistency of the scrotal mass. Without anesthesia an anterior longitudinal scrotal incision was carried through the scrotal tunics. The tunica vaginalis testis was entered and no bloody fluid or clot was present. A line of cleavage was obtained between the mass and the parietal layer of the tunica vaginalis with slight difficulty except at one area where a strip of capsule on the anterior border of the mass remained densely adherent to the parietal layer of the tunica vaginalis. The mass was dark red in color, symmetrical in contour and the size of a large green olive. The spermatic cord was glistening in appearance, was not discolored or edematous and entered

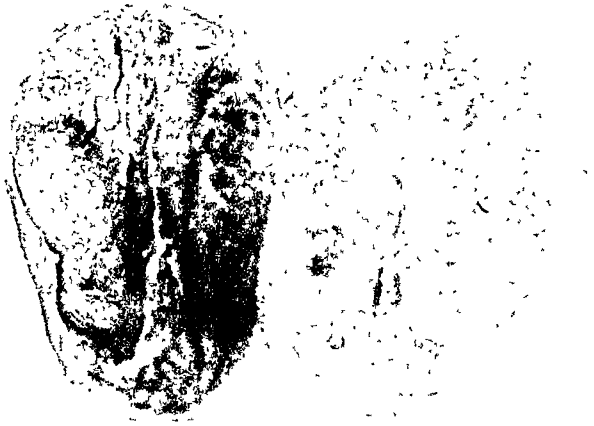

FIG. 1. Section of testicle shows marked enlargement, obliteration of parenchymal markings and mottled, hemorrhagic appearance.

the posterior border of the mass. The investment of the parietal tunica vaginalis was high on the spermatic cord. There was no gubernaculum or mesorchium. No twist in the intravaginal or extravaginal portion of the spermatic cord was demonstrable. The epididymis could not be identified. A longitudinal incision was then made into the mass on its anterior border to determine the presence of testicle within a possible organized hematocele clot. The entire surface of the cut section of the mass was firm, granular and dark red with no evidence of normal testicle. The cut section of the mass resembled an organized blood clot. No bleeding resulted from incision into the mass. The intravaginal portion of the spermatic cord was incised between clamps, and the mass and attached portion of the spermatic cord were removed. The postoperative course was uneventful, and the infant was discharged on the second postoperative day.

Pathological report (Dr. Edwin H. Albano): The testicle was enlarged and measured 4.9 cm. in its longest diameter (fig. 1). The surface was smooth and glistening except for small scattered tabs of pale yellow fatty tissue attached. The tunica was congested. On section the parenchymal markings are obliterated, and the tissue had a mottled, reddish-black, solid hemorrhagic appearance. Dark, thick fluid blood could be expressed from the cut surfaces.

Microscopic description (figs. 2 and 3): The chief pathological process was one of diffuse hemorrhagic infarction. The major portion of the testicular parenchyma was destroyed and replaced by extensive hemorrhage. Many of the erythrocytes lay in pools of edema fluid and laked blood. The few remaining tubules possessed a juvenile type of epithelium showing complete absence of spermatogenic differentiation. Some of the tubules had a pale, washed-out, ghost-like appearance.

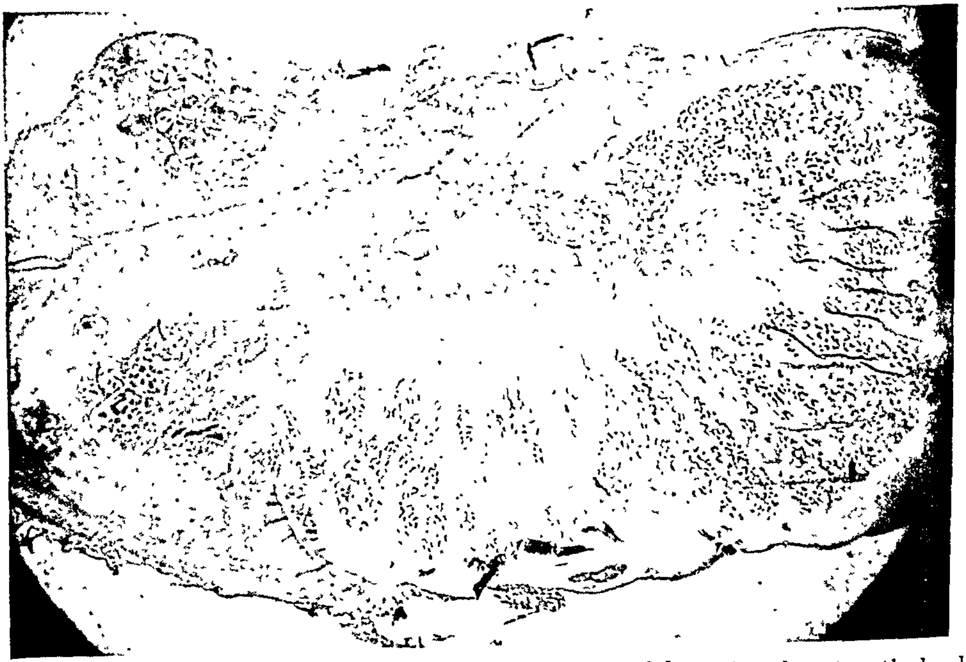

FIG. 2. Microscopic section reveals parenchyma of testicle to be almost entirely destroyed and replaced by extensive hemorrhage.

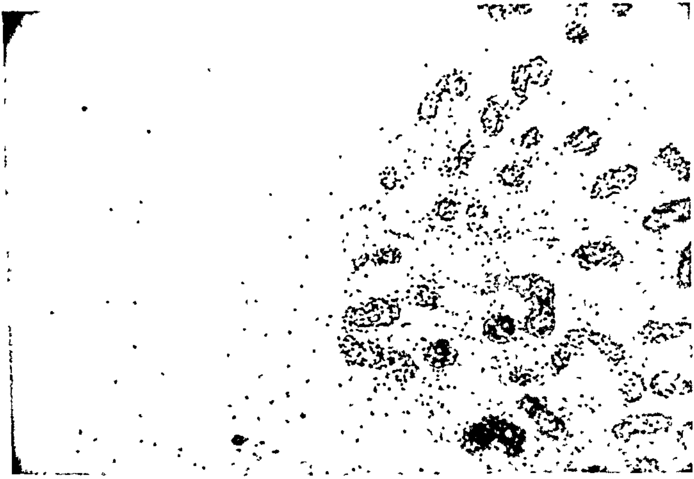

FIG. 3. Microscopic section discloses few scattered tubules that possess juvenile type of epithelium and complete absence of spermatogenic differentiation.

Bizarre tubular fragments and the remains of numerous pyknotic cell nuclei, as well as a few polymorphonuclear leukocytes and histiocytes, were scattered throughout. The tunica overlying the area of infarction was congested and necrotic. A moderate amount of fibrin was deposited in the adjacent tissue. Diagnosis: Hemorrhagic infarct of the testicle.

DISCUSSION

Bluish discoloration of a smooth, globular enlargement of the hemiscrotum is the outstanding clinical characteristic of idiopathic hemorrhagic infarct of the testicle in the newborn. The thin, delicate scrotal tunics of the newborn provide transparency to the purplish-red gangrenous testicle that is not usually seen in the child or adult. The degree of scrotal tenderness and edema would vary according to the time of occurrence of the process of hemorrhagic infarction during intra-uterine existence, labor or the neonatal period. Fever is mild. With the advance of time the scrotal wall becomes less edematous and is later adherent to the testicular mass which is firm and nontender.

The differential diagnosis of idiopathic hemorrhagic infarct of the testicle should be less difficult in the newborn than in infancy, childhood and adult life since epididymitis, orchitis and torsion of the spermatic cord and of the testicular and epididymal appendices are far more common after the neonatal period. Tumors of the scrotal contents, other than tumor testis, are very rare in the newborn. Tumor of the epididymis in the newborn has been reported.[8] The presence of scrotal masses requires consideration of such conditions as orchitis, due to mumps, trauma or syphilis, acute and chronic epididymitis, nonspecific, gonococcal or tuberculous, hydrocele and hernia. Testicular tumor, hematocele and hemorrhagic orchitis comprise diseases which are most difficult to differentiate.

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[8] Burros, H. M. and Mayock, P. P. Adenomatoid tumor of the epididymis Report of a case in a newborn. J. Urol., 63: 712, 1950.

Tumor testis presents unilateral discolored enlargement of the scrotum which might contain bloody fluid within the vaginal sac and is otherwise a firm, freely movable, nontender heavy mass. Supraclavicular lymph nodes and an epigastric mass may be palpable with x-ray evidence of lung metastases and positive Aschheim-Zondek test. Exploration biopsy may be the only possible method of diagnosis.

Primary or secondary hematocele is characterized by a smooth, globular, discolored mass which does not transilluminate light and often follows injury. Trauma incident to labor is not easily established in such cases.

Hemorrhagic infarct of the testicle due to torsion of the cord and spontaneous untwisting of the cord would be indistinguishable from idiopathic hemorrhagic infarct of the testicle since an elevated position of the testicle would not be present.

Hemorrhagic orchitis results from trauma to the testicle or interference with its blood supply. Obstetrical hemorrhagic infarction of the testicle may follow severe hemorrhagic or traumatic orchitis incurred during labor. The presence of a testicular mass at birth, however, would require serologic test to rule out syphilis and exploration biopsy to rule out neoplasm.

COMMENT

The pathological nature of this disease of the testicle in the newborn establishes a process of circulatory deprivation of the testicular parenchyma. In spite of the multiple source blood supply of the testicle no other parenchymatous organ is more vulnerable to acute complete circulatory occlusion and total necrosis. Although it is assumed that surgical untwisting of the spermatic cord within three hours from the onset of torsion will restore the blood flow to the testicle and salvage its structural and functional integrity it might not be presumptuous to regard occlusion of the vascular supply of the testicle in the newborn beyond fifteen minutes as capable of producing irreversible damage to the testicle.

Etiology of this condition is probably related to topographical variations of the scrotal contents. It is not without significance in the case herein cited that the parietal layer of the tunica vaginalis testis was found invested high on the spermatic cord, that there was present a long intravaginal segment of the spermatic cord and that there was no gubernaculum or mesorchium. Pathological evidence of organization of the inflammatory process within and about the testicle and adhesions of nonedematous scrotal tunics would place the onset of the process of infarction during intra-uterine existence or during labor which was uneventful. The diagnostic problem that presents in such cases demands surgical intervention not only for the purpose of possibly decompressing an hematocele to spare the testicle from pressure atrophy or performing orchiectomy for hemorrhagic infarct but for the purpose also of accomplishing exploration biopsy or orchiectomy in the possible presence of testicular tumor.

SUMMARY AND CONCLUSIONS

Bluish discoloration of a smooth, globular enlargement of the hemiscrotum is the outstanding clinical characteristic of idiopathic hemorrhagic infarct of the testicle in the newborn

Hematocele and testicular tumor are difficult to differentiate from hemorrhagic infarct of the testicle

Surgical exploration is indicated for the purpose of accurate diagnosis and accomplishment of required surgical treatment

The etiological basis of the development of testicular infarction probably lies in the anatomical variations of the scrotal contents Trauma, exertion, labor, inguinal surgery and the presence of inguinal masses provide influences which when superimposed upon topographical deviations of the testicle, spermatic cord and their tunics are capable of invoking complete or temporary circulatory occlusion of the vascular channels and irreversible damage to the testicle

Obstetrical hemorrhagic infarction of the testicle during the process of normal labor is apparently far more common than is generally appreciated and probably accounts for many cases of unexplained testicular atrophy seen in the adult

The fifth case of hemorrhagic infarct of the testicle in the newborn in the absence of a demonstrable cause is reported

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EPIDERMOID CYSTS OF THE TESTICLE

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From March 1951, through January 1953, eighty cases of testicular tumor were treated in the urological service of Walter Reed Army Hospital. Two cases of epidermoid cysts of the testicle and one of adult teratoma were included in this series. The latter is reported because it clinically resembled and was grossly largely composed of an epidermoid cyst. A review of the literature reveals that only five cases of epidermoid cysts of the testicle have been reported. One was reported by Dockerty and Priestley[1] in 1942, one by Gage and Brodie[2] in 1950, two by Mooslin and Schulte[3] in 1951, and one by Jensen[4] in 1952. Although the pathology has been well described, the etiology is still in controversy.

All testicular tumors are considered malignant until proved pathologically to be benign. In the following cases a diagnosis of benign tumor was made on the basis of bimanual palpation of the testicle. The tumors were small, ovoid, discrete, smooth, firm, and slightly mobile within the testicle.

In each case surgery was carried out through a scrotal incision. After removal of the tumor from the testicle, the tunica albuginea was approximated and the scrotum closed with drainage.

CASE REPORTS

Case 1.—A 29-year-old white man was admitted to Walter Reed Army Hospital on March 8, 1951. The patient had noticed a firm nodule in his left testicle for 5 years. Because of tenderness in the testicle of a few months' duration he reported to the hospital. Physical examination was unremarkable except for the nodule in the superior pole of the left testicle. Incision of the tunica albuginea revealed a 1.2 cm. firm tumor well encapsulated in a glistening white membrane and which easily shelled out of the surrounding normal testicular tissue. On section, the tumor contained a pale tan material arranged in concentric lamellae. Microscopic sections (fig. 1, *A*) revealed a cyst in which most of the wall was denuded, but where it was present it consisted of squamous epithelium. The lumen of the cyst contained keratin. The pathological diagnosis was epidermoid cyst of the testicle.

Case 2.—A 24-year-old white man was admitted to Walter Reed Army Hospital on October 20, 1952. A few days earlier while the patient was being processed for discharge from the Army, the examining physician found a nodule in his right testicle. This nodule had not been noticed by the patient nor had it caused symptoms. Physical examination was unremarkable except for the nodule in the superior pole of the right testicle. Incision of the tunica albuginea revealed a

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[1] Dockerty, M. B. and Priestley, J. T.: J. Urol., **48:** 392–400, 1942.
[2] Gage, A. A. and Brodie, E. L.: J. Urol., **63:** 539–541, 1950.
[3] Mooslin, K. E. and Schulte, J. W.: Calif. Med., **74:** 435–437, 1951.
[4] Jensen, O. J. Jr.: J.A.M.A., **149:** 109–113, 1952.

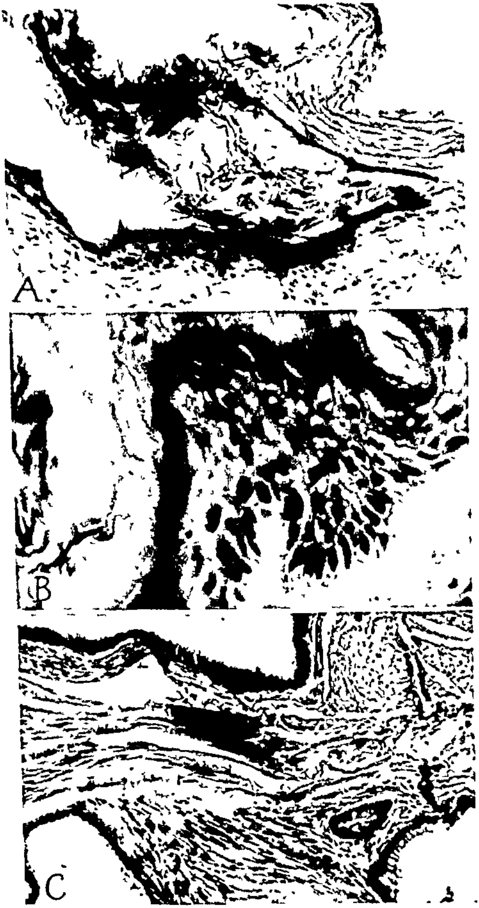

FIG. 1

1.2 cm. white, firm, smooth, ovoid tumor which was easily shelled out of the surrounding normal testicular tissue. On section, the wall of the cyst measured less than 1 mm. in thickness and contained a yellowish friable looking material. Microscopic sections (fig. 1, *B*) revealed the lining of the cyst to be composed of a thin layer of squamous epithelium. The squamous epithelium was clearly demarcated from the surrounding normal testicular tissue by a thin layer of fibrous tissue. The lumen contained keratin. The pathological diagnosis was epidermoid cyst of the testicle.

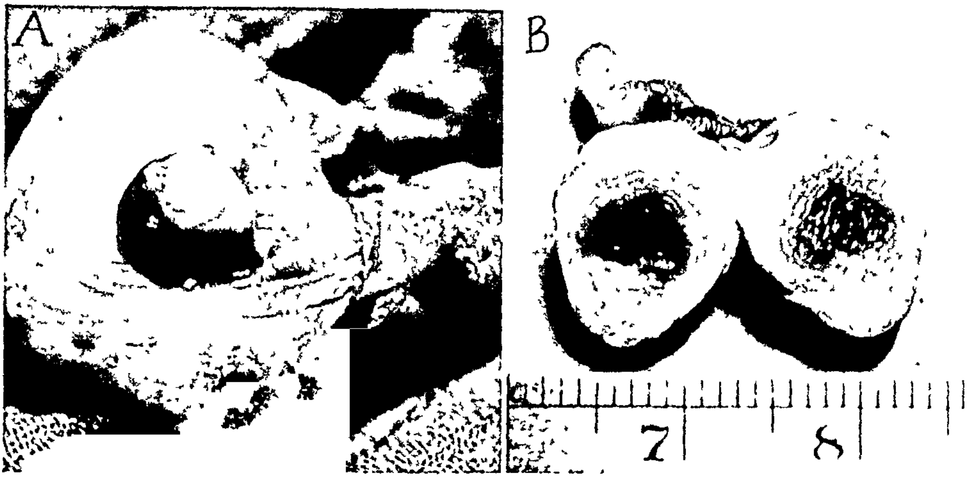

FIG. 2

Case 3.—A 22-year-old white man was admitted to Walter Reed Army Hospital on January 17, 1953. The patient had noticed a small nodule in his left testicle one year prior to admission. This nodule was found during a physical examination for a regular Army commission and the patient was referred to the hospital. Physical examination was unremarkable except for the nodule in the medial and superior portion of the left testicle. Incision of the tunica albuginea (fig. 2, *A*) revealed a 1 cm. white, ovoid, firm tumor which was well encapsulated and easily shelled out of the surrounding normal testicular tissue. At one edge of the tumor (fig. 2, *B*) was a cystic structure measuring 0.5 cm. in length. On section, the larger cyst contained a laminated yellowish-tan material, in the center of which was a brown discoloration. The smaller cyst contained a lipoid-mucoid material. Microscopic sections (fig. 1, *C*) revealed the lining of the larger cyst to be squamous epithelium with a granular cell layer. The content of the cyst was laminated keratin. The smaller cystic structure was composed of cysts lined by ciliated respiratory-type epithelium and mucus secreting intestinal-type epithelium. The pathological diagnosis was adult teratoma of the testicle.

SUMMARY

Two cases of epidermoid cysts of the testicle and one case of adult teratoma of the testicle have been presented because of their rare occurrence.

The authors are indebted to Col. Joe M. Blumberg, chief of pathology, Walter Reed Army Hospital for the microscopic descriptions of the tumors.

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SCLEROSING LIPOGRANULOMA OF THE SPERMATIC CORD

LOWRAIN E. McCREA

Sclerosing lipogranuloma is considered to be a peculiar granulomatous reaction in the fatty tissues. Ash and Friedman first called attention to the condition affecting the organs of the genito-urinary system, and called the condition sclerosing lipogranuloma. In 1948 Powell and Powell presented a case affecting the genitalia. Smetana and Bernhard in 1950 presented a classical description of the condition, reviewed the literature and presented 7 cases. Since 1950, two other investigators have presented cases typical in the histological picture, bringing the total number of cases affecting the genito-urinary system to thirteen, including the case to be presented. It is the purpose of the presentation to consider sclerosing lipogranuloma as it affects the spermatic cord and to review the literature of the condition as it affects the organs of the genito-urinary system. It has also been established that sclerosing granuloma is not always confined to the organs of the genito-urinary system but is known to occur in many other structures.

Because of the peculiar tissue reaction, the condition has been called by various terms, among which are saponifying necrosis, necrosis of subcutaneous fat tissue, ischemic fat necrosis, lipogranuloma, lipodystrophy, lipophages *granuloma, adiponecrosis, lipoid necrobiosis. The term sclerosing lipogranuloma* as used by Ash and Friedman is now considered standard.

The pathogenesis of sclerosing lipogranuloma is not known. The condition is believed to usually follow trauma. Grossly, the pathological appearance, according to Smetana and Bernhard, is characterized by disruption of adipose tissue, the presence of cystic spaces of various sizes filled with fluid or fatty material and scarring of varying density. These investigators conclude that following trauma "the essential consequence is not physical disruption but rather transformation of physiologic fat into a mildly irritating unphysiologic substance with which the body can cope only by transportation, segregation, and walling off from the normal tissue."

Analysis of the history of the cases presented and the microscopic specimens revealed that sclerosing lipogranuloma is a reaction of adipose tissue to trauma which is utterly different than the reaction of other tissues to trauma. Analysis further reveals that several had a definite and direct history of trauma while others presented a case history of a local inflammatory reaction. All cases showed a definite tendency to progress once the inciting element of the granulomatous reaction was established. Whether or not this reaction of adipose tissue is the result of a temporary interference of local blood supply and fat metabolism is not clear. It is established that lipogranuloma tends to continue when the process is once inaugurated. Spontaneous healing is slow and it is doubtful if it ever occurs. Undoubtedly this continued advancing process accounts for the

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Read at annual meeting, Mid-Atlantic Section, American Urological Association, Roanoke, Va March 12–14, 1953 numerous discordant interpretations of the physical and pathological findings that have been presented by numerous investigators.

The condition has been observed in the white and colored races and in both sexes. The age of the individuals affected varies in the reported cases from 20–60 years. Duration from onset to operation varies from 3 weeks (the case herein reported) to 8 years. Analysis of the reports in the literature reveals that the condition has affected the tissues of the scrotum in 3 instances; the penis twice; the scrotum and penis on 2 occasions; the epididymis, perineum, and the periurethral tissues once. Ordinarily tissue reaction quite quickly follows trauma. However, it will be noted that in some instances of sclerosing lipogranuloma, the condition has been slowly progressive for a period of years. Regardless of its position it has been shown that an inherent tendency to progress exists and there is only one method of treatment, namely, excision.

There is one important factor regarding sclerosing lipogranuloma that is yet to be explained. Trauma to adipose tissue is common, while the occurrence of sclerosing lipogranuloma is relatively rare. Therefore, basically, there must be some underlying inherent causative factor, accompanying trauma or inflammatory reaction producing the condition.

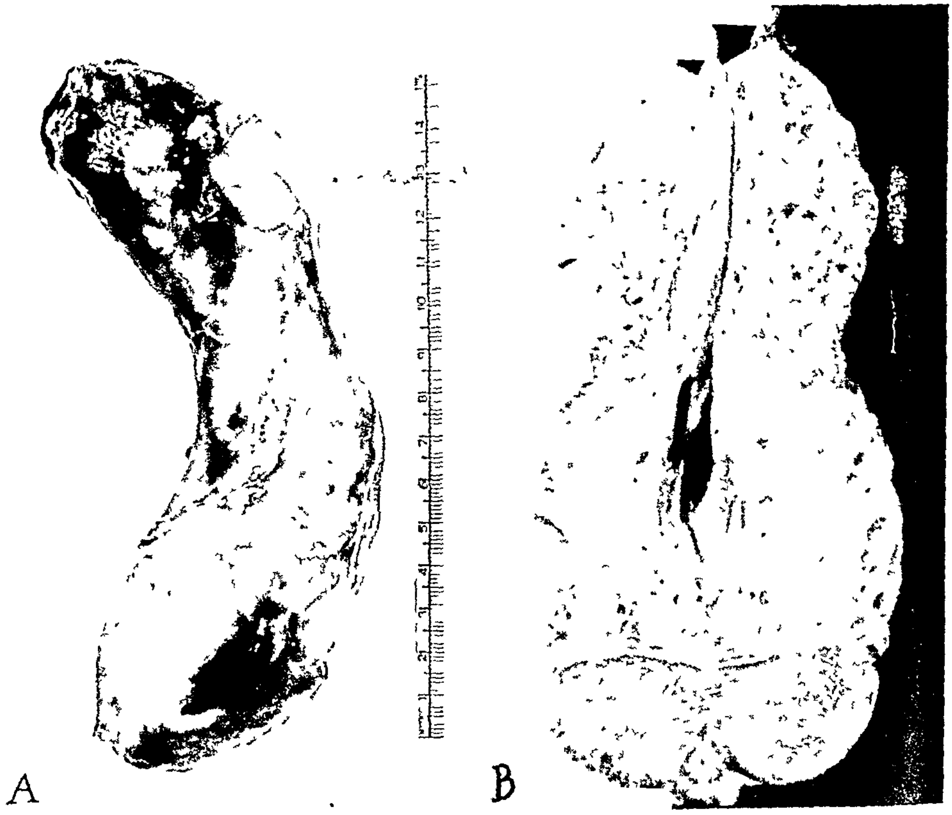

FIG. 1. *A*, large, cylindrical, painless mass extending from internal inguinal ring into scrotum Mass, although movable, appeared fixed to surrounding tissue *B*, note almost complete obliteration of structures of spermatic cord by fatty tissue Testicle appears grossly normal

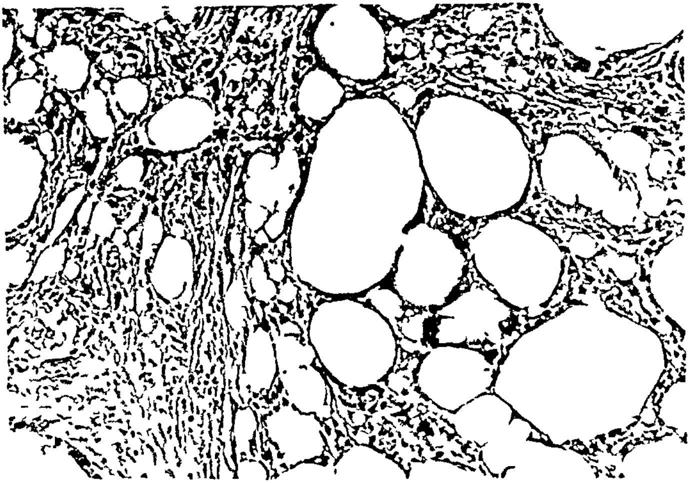

FIG 2 Background of fibrofatty tissue Fat lobules are distorted and in some areas disclose microcystic dilatation Microcysts are lined by lipid laden macrophages or giant cells of foreign body type Stroma is sprinkled by lymphocytes macrophages, eosinophiles and giant cells

CASE REPORT

A white man 59 years of age was readmitted to the hospital 3 months following abdominoperineal proctosigmoidectomy for carcinoma of the sigmoid There was present a painless, increasing, cylindrical mass involving the left spermatic cord (fig 1, *A*) This mass was not apparent before proctosigmoidectomy It was first noticed 3 weeks following surgery The patient refused intervention for the removal of the mass at that time, but as the mass continued to increase in size he agreed to surgery for its removal (fig 1, *B*) The spermatic cord was ligated at the level of the internal inguinal ring and the mass including the testicle was bluntly dissected from the scrotum The postoperative course was uneventful Diagnosis Sclerosing lipogranuloma of the spermatic cord (fig 2) This patient was seen February 2, 1953, eight months following the removal of the sclerosing lipogranulomatous mass, at which time a hard, cylindrical mass was palpable at the internal inguinal ring This mass, according to the patient, is not painful but is gradually increasing in size

SUMMARY

Sclerosing lipogranuloma is a reaction of fatty tissue which occasionally follows trauma The process of the reaction is not known but is believed due to interference of local blood supply and fat metabolism Spontaneous healing of sclerosing lipogranuloma is slow, if it ever occurs Once established there is an apparent tendency to continued progression. The only known treatment for sclerosing lipogranuloma is excision. A review of the reported cases affecting the organs of the genito-urinary system is presented together with the addition of a personally observed case.

CONCLUSION

An apparent unexplained inherent causative factor accompanying trauma of inflammatory reaction tends to produce sclerosing lipogranuloma.

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SEMINAL TRACT CALCULI

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Several articles in the urological literature of the past 2 years have called attention to calcification of the seminal vesicles and ampullary portions of the vasa in association with diabetes mellitus This calcification has been demonstrated to consist of calcific deposits or replacement within the muscular walls of these organs

A careful search of the literature for at least the past 50 years, however, has failed to reveal a report of discrete calculi within the canals of the seminal tract A short paragraph in Keyes' *Textbook of Urology* refers to "sandy" deposits found in the seminal vesicles in autopsy specimens but other than this no reference to seminal calculi can be found It is my purpose here to report 2 cases of such "seminal calculi"

CASE REPORTS

Case 1—Mr F Z first presented himself in March 1942 at the age of 34 complaining of dull, aching suprapubic pain of 8 years' duration Cystoscopic examination was negative except for evidence of posterior urethritis Treatment with prostatic massage failed to give relief and, after a short time, treatment was discontinued He re-appeared in October 1945 with the same symptoms plus a urethral discharge and terminal hematuria The same diagnosis was made and the same treatment given The urethral discharge and the terminal hematuria ceased but the suprapubic and perineal pain persisted At this time a palpable calculus in the left side of the prostate was noted and confirmed by x-ray (fig 1)

In March 1950 he was admitted to the hospital for surgical removal of this calculus At this time, on cystoscopic examination, it was noted that pressure over the stone by a finger in the rectum caused a jet of bloody material to escape from the orifice of the left ejaculatory duct The bladder and upper urinary tract were normal except for duplication of the left kidney pelvis and ureter

The prostate was exposed through a perineal incision and the large stone was readily palpated in a superficial position in the left half of the gland An incision was made over it and it was removed It was noted that it lay in a cavity which appeared to be lined with mucous membrane and it was found that a probe could be passed readily in both directions from the cavity There seemed little doubt but that this stone lay in a greatly dilated portion of the left ejaculatory duct

The perineal wound healed cleanly and he was discharged from the hospital on the seventh postoperative day

For about 6 months he was completely free of symptoms but the dull suprapubic ache recurred and had continued intermittently to date of admission although never so severe as before the stone was removed Recent x-rays had shown no evidence of recurrent calcification and a seminal vesiculogram showed

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Read at a meeting of the New England Section, American Urological Association, April 30, 1953

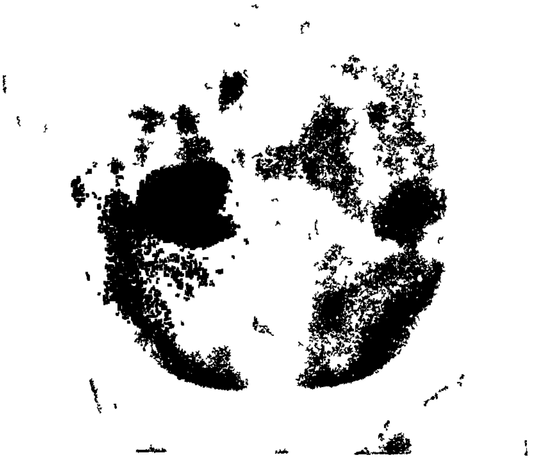

FIG. 1. Case 1. Large calculus in prostatic area which proved to be within ejaculatory duct.

free drainage from both sides with apparently normal seminal tracts. The prostatic secretion became normal and a semen specimen was normal in all respects.

Case 2—P. D. was a 20 old boy when he first came under observation in February 1948. At that time he was admitted to the Hartford Hospital with a story of acute onset of very severe right abdominal pain. He was writhing all over the bed, retching, vomiting and complaining of agonizing right abdominal pain which seemed colicky in nature. There was marked right abdominal spasm and tenderness and some tenderness in the right costovertebral angle. His white blood count was 12,000, 84 per cent polymorphonuclear neutrophils. His urine contained 3–5 red blood cells per high power field. There was slight right rectal tenderness. The presumptive diagnosis was right ureteral colic but an excretory

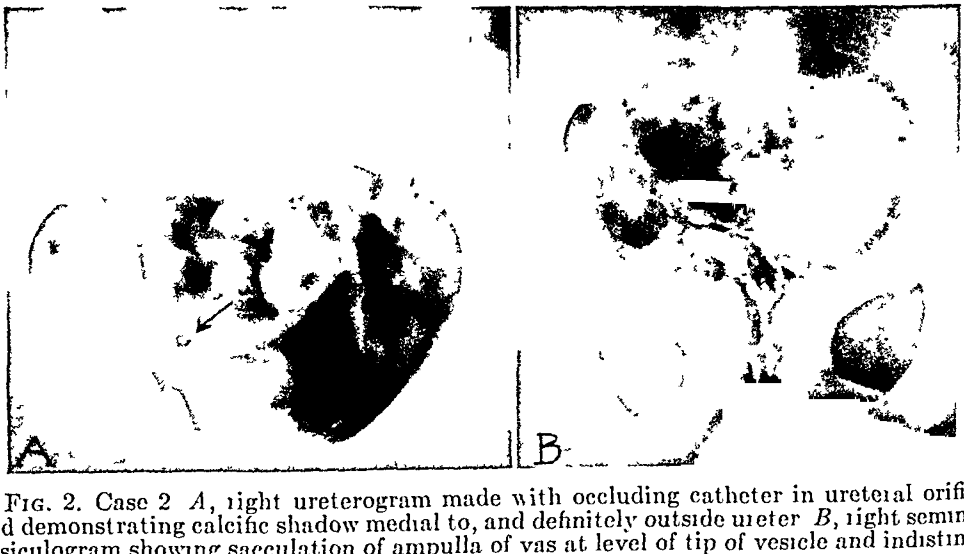

FIG. 2. Case 2 *A*, right ureterogram made with occluding catheter in ureteral orifice and demonstrating calcific shadow medial to, and definitely outside ureter *B*, right seminal vesiculogram showing sacculation of ampulla of vas at level of tip of vesicle and indistinct filling defect in saccule

urogram was negative and an appendectomy was done with removal of a normal appendix. The surgeon who treated him at that time felt when he discharged him that he had probably had a right ureteral calculus that had passed spontaneously.

In July 1948, five months later, he was re-admitted for study with the story that he had continued to have attacks of right abdominal pain 5 or 6 times a month. These attacks were always acute in onset, bore no relation to any particular sort of activity and lasted usually a day or two. They continued to be very severe. Cystoscopy showed acute and chronic posterior urethritis, normal upper urinary tracts with a calcific shadow in the right side of the pelvis which was definitely extra-ureteral (fig. 2, *A*). Chest x-ray was negative. Barium enema, gastro intestinal series with small bowel studies and cholecystogram were negative. It was observed that there was a little thickening in the region of the right seminal vesicle and definitely increased tenderness here. Treatment by prostatic massage and vesicular stripping gave no relief and was discontinued after a trial.

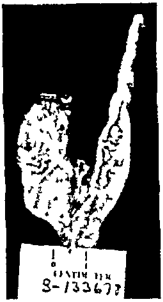

Fig. 3. Case 2. Right seminal vesicle and ampullary portion of right vas deferens with calculus.

During the next 3 years the patient was at college in Vermont and was seen only rarely though he continued to have attacks of severe colic at irregular intervals. These were of such severity that he usually landed in a hospital where the work up was inconclusive and the attack subsided. At various times he was studied at several large hospitals and at least two famous New England diagnostic centers. He returned finally to Hartford where recurring attacks of pain often called his doctor out in the middle of the night to administer sedatives. By this time the young man began to feel that his future was being blighted by this mysterious malady that kept him from work for a day or two several times a month. His doctor, on the other hand, was torn between a certainty that there was an organic cause for the symptoms and a growing conviction that he was dealing with a bizarre manifestation of psychoneurosis.

In February 1952, four years after the first attack, the patient was again admitted to the hospital for study. By this time it seemed probable that the symptoms were due to chronic seminal vesiculitis with an exaggerated reaction to pain. He was again subjected to complete diagnostic study. A psychiatrist felt that he was a normal young man who was only justifiably worried by his infirmities. A seminal vesiculogram showed an essentially normal seminal tract on the right side except for a peculiar sacculation in the ampulla of the vas that was at first thought to be of little importance (fig. 2, *B*). Puzzling over the problem one day, the forgotten "extra-ureteral calcific shadow in the right side of the pelvis" came to mind and, when a film in which this shadow appeared was superimposed on the right seminal vesiculogram, the shadow fell into the sacculation of the ampulla of the vas and the diagnosis of vasolith was made.

The right seminal vesicle, together with the ampullary portion of the right vas with its contained stone, was removed through a perineal approach (fig. 3). The wound healed well. The patient was discharged in 10 days and in a year and a half he has had no more pain, he has been married and he has this month become a father.

In both of these cases diagnosis and definitive treatment were too long delayed because of ignorance of the possibility of seminal calculi. With the knowledge of the possibility of having stones in the seminal tract one can be sure that pelvic "phleboliths" will be viewed with a little more suspicion in obscure cases henceforth. In like fashion one could criticize the vasectomy and vesiculectomy in the second case when it is quite possible that vasolithotomy alone would have sufficed. The only defense again is ignorance of the disease process and the desire to insure relief from recurrent painful and disabling episodes in a young man who was rapidly reaching the end of his endurance.

One can only speculate on the subject of etiology. The stone in the second case was analyzed and found to consist of carbonate apatite (carbonated calcium phosphate). It would seem likely that inflammation or congestion had prompted bleeding with retention of a small clot which became calcified instead of being evacuated or absorbed.

In conclusion, 2 cases of obscure abdominal pain due to discrete calculi in the seminal tract have been described. So far as can be determined this entity has not previously been reported.

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CORTISONE THERAPY IN OSTEITIS PUBIS

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Osteitis pubis was first described as an entity by Edwin Beer in 1924. In 1945 Muschat reported a series of 25 cases collected from the literature and reported with these his own 2 cases. The great majority of these followed prostatectomy by the suprapubic route, however, others have reported the development of osteitis pubis following other operative procedures. Wilensky reported 2 cases in women, one which followed a symphysiotomy and the other appeared after a normal delivery. A vaginal fistula developed originating at the os pubis. In a third case appearing in the female, the clinical picture of osteitis pubis was reported by Kleinberg. This infection was apparently metastatic, the source being pyelonephritis.

In 1923 Barnes reported the clinical picture of osteitis pubis following a perineal prostatectomy. The clinical picture has also been reported following an infected inguinal hernia repair. Wheeler, in 1941, reported extensive invasion of the os pubis following suprapubic cystostomy. The clinical picture has also been found with a prostatic abscess, and with occupational trauma to the lower abdomen.

Following Millin's introduction of prostatectomy by the retropubic approach in 1946, osteitis pubis became one of its accepted hazards. Beneventi, a staunch advocate of this procedure, suggested that this complication may be due to disturbance of the blood supply to the os pubis. Most workers agree that the two requisites for this clinical picture are trauma and infection. The large percentage increase in this complication following the advent of retropubic prostatectomy lends support to this view. The case of trauma to the periosteum of the pubis while working in the limited prevesical space is obvious. Great care must be used in the handling of retractors and surgical needles. The ever present infection in any prostatic surgery is the second requisite.

PATHOLOGY

Although many workers have studied the pathology of osteitis pubis, the picture is still not clear. Goldstein, by means of a biopsy of the pubic bone, in one of his cases, described the pathology as showing the presence of loose cellular connective tissue within the marrow spaces. This connective tissue was infiltrated with polymorphonucleocytes, lymphocytes, and a few histiocytes. The fragments of bone at biopsy were softer than those of normal bone. The pathological diagnosis was reported as "fragments of bone showing a histologic picture compatible with the diagnosis of osteitis."

Pierson reported biopsy of the bone in one of his patients as showing a chronic inflammatory reaction. Silver reported his biopsy as showing a nonspecific acute, inflammation. Wheeler, however, was of the opinion that osteitis pubis is a result

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Read at annual meeting, Mid Atlantic Section, American Urological Association, Roanoke, Va. March 12–14, 1953.

of nerve injury. He reported one case in which at autopsy there was no inflammatory process, but an atrophy of the cellular elements of the bone was found. Osteitis pubis was classified by him as a form of Sudeck's atrophy. This atrophy originally was described by Sudeck in 1900.

SYMPTOMATOLOGY

Clinically, the symptoms rarely appear less than 10 days following surgery, and usually within 2 to 6 weeks. The symptoms are manifested by a gradual onset of pain and tenderness over the body or rami of the pubis or ischium. This is followed by pain along the inner and outer aspects of the thighs and occasionally in the perineum. There is increasing pain in the groins on walking and later painful spasm of the adductor muscles of the inner thigh. The patient usually is confined to bed. There may be painful defecation or urination due to spasm of the levator ani and levator perinei, both of which are attached to the periosteum of the pubis. The course is usually febrile, and persists for several weeks. The disease is self-limiting, the pain and tenderness usually lasting from six to eighteen months.

RADIOLOGY

Radiologically, there may be no findings in the early stages. The first noticeable change is a fuzziness or haziness in the pubis or its rami. This is followed by a frayed appearance of the periosteum, most commonly along the descending rami. This is followed within 2 or 3 weeks by a moth-eaten appearance of bone destruction in the pubic rami. In late stages there may be a separation of the symphysis due to a destruction of the cartilage. Healing may be characterized by spur formation, ossification of the symphysis, or by healing and restitution of new bone.

TREATMENT

Since recognition of osteitis pubis as an entity, different clinicians have suggested various types of treatment. Most workers agree that until the advent of adrenocorticotrophic hormone (ACTH) and cortisone, all of the recommended treatment left something to be desired. Treatments in vogue were diathermy, radiation therapy, chemotherapy and antibiotics. On the presumption that osteitis pubis was a trophic disease, large doses of vitamin B complex have been used. Frequently orthopedic treatment such as splints, traction, novocain injection, obturator crush, and physiotherapy have been beneficial in relieving pain. Hock and Kurtz stress the importance of removal of foci of infection. This is done by lavage of prevesical space with solutions containing antibiotics either by introduction through a catheter or needle. Recently Marshall and his group have reported encouraging results from ACTH. Daw also reports gratifying results with the use of cortisone.

CASE REPORTS

Case 1. A 65 year old Negro was first seen in January 1952 with symptoms of prostatism. Urological studies revealed benign hypertrophy of the prostate and stricture of the anterior and membranous urethra A flat radiograph of the abdomen, at that time, did not reveal any disease of the bones of the lower abdomen and pelvis Transurethral prostatectomy was performed and the patient made an uneventful recovery The urethral stricture was dilated in early May and on June 1 in the office Following the second dilatation, the patient returned to his home in a nearby town. Subsequently acute urinary retention developed His physician unsuccessfully attempted to pass a catheter and he was referred to the hospital in acute urinary retention

On admission the clinical picture was that of urinary extravasation A suprapubic cystostomy was done and an indwelling urethral catheter inserted The suprapubic tube was removed 4 days postoperatively and the urethral catheter removed 5 days later. He had an uneventful postoperative course and returned home on June 29, 1952 Six days later he was again admitted to the hospital complaining of marked pain in the right inguinal region, groin, and both testicles The pain was sufficiently severe to prevent him from walking

On physical examination the positive findings were tenderness on light pressure over the pubic bone and lower abdomen This was accompanied by pain on adduction of both thighs His temperature was 99 8F The urinalysis showed a trace of albumin and microscopically revealed many red blood cells His blood studies were essentially normal except for a hemoglobin of 65 per cent and a red blood count of 3,200,000

The clinical picture was one of osteitis pubis The patient was immediately placed on 300,000 units of duracillin daily and 0 5 gm of dihydrostreptomycin twice daily intramuscularly This was supplemented by sulfamerazine by mouth and diathermy to the painful area After approximately 2½ weeks of this therapy only slight improvement was noted both objectively and subjectively At that time all therapy was discontinued A flat radiograph of the lower abdomen was reported as showing multiple confluent areas of bone destruction of the bodies of both pubic bones adjacent to the symphysis involving especially the posterior halves of both pubic bodies (fig 1, A) He was then placed on cortisone· 300 mg the first day, 200 mg the second day and 100 mg daily for 10 days After a few days of this therapy, the patient began to improve markedly At the end of the 12 days of cortisone therapy he was free of pain, his temperature was normal, and there was no evidence of tenderness on pressure over the involved areas See figure 1, *B*

After completion of cortisone therapy a re-examination of the lower abdomen was done by radiograph which was reported as showing complete regeneration of both pubic bones without residual areas of bone destruction The patient was discharged 3 days later apparently free of all symptoms of osteitis pubis He was advised to return for follow-up urethral dilatation This advice he has not followed

Case 2 This case report is offered by Dr R M Bobbitt et al A 74 year old white man underwent a suprapubic prostatectomy for benign hypertrophy of the prostate on September 22, 1952 Four weeks following surgery pain developed

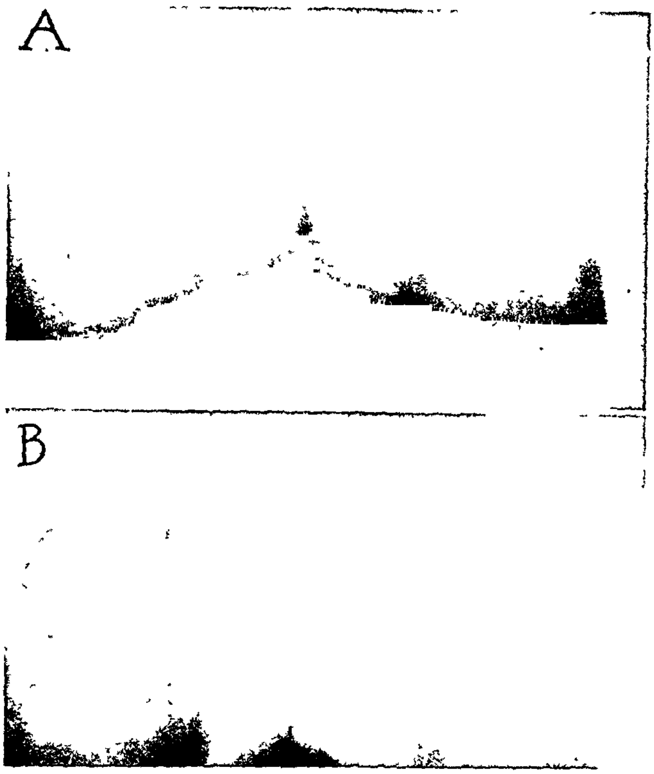

FIG. 1. Case 1. *A*, x-ray several weeks after suprapubic cystotomy for ruptured urethra and day prior to cortisone therapy. Marked decalcification of both pubic bodies, more marked adjacent to symphysis, with complete destruction of medial cortex of both pubic bodies. *B*, after 12 days of cortisone therapy. Complete regeneration of both pubic bodies except for small triangular destroyed area in right superior pubic body.

in the pubic region and thighs, and the patient had difficult in walking. The clinical picture of osteitis pubis progressed rapidly. The adductor spasm became so marked that the thighs could not be separated. A flat radiograph taken on December 17, 1952 revealed the moth eaten appearance of the pubic rami, consistent with a diagnosis of osteitis pubis.

The patient was placed on cortisone therapy, 100 mg. for 2 days, followed by 50 mg. a day for 1 week, then 25 mg. a day for 30 days. Within 24 hours after beginning cortisone, marked subjective improvement followed. The patient was able to walk without pain after 3 days of treatment. After 10 days of cortisone he was free of symptoms.

DISCUSSION AND CONCLUSION

A brief review of the literature on osteitis pubis has been given. Two additional cases are reported because of dramatic response to cortisone therapy. The diagnosis was confirmed by radiographic evidence. The first case also was of interest because of its unusual causative factor. The second case was of interest because of the rapid disappearance of subjective complaints.

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CARCINOMA IN MALDESCENDED TESTES

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We wish to report 3 cases of carcinoma occurring in undescended testes. One of these, torsion of an intra-abdominal testicle with associated malignancy, is of particular interest because of the few cases published.

CASE REPORTS

Case 1. R. O., Mercy Hospital No. 6410, a 20 year old white man, was seen on October 12, 1950 because of sudden excruciating pain arising in the lower left quadrant and radiating to the scrotum and left thigh. Since the onset of the pain, the patient had not been able to urinate. There was no history of previous urinary difficulties.

On physical examination, the abdomen was acutely tender and rigid in the lower left quadrant. The left testicle was not present either in the scrotum or inguinal canal. The patient was catheterized with ease and 1½ ounces of clear urine obtained. Urinalysis and complete blood count were normal. Kahn test was negative. A plain x-ray showed the kidney and psoas shadows to appear normal. No evidence of calculus was seen.

A diagnosis of torsion of an intra-abdominal testicle was made. Through a left pararectus incision the peritoneum was opened, and a torsed mass, the size of an orange, was found overlying the bladder. An epididymis-like structure and a vas deferens were present in a small peritoneal pouch occupying the left portion of the scrotum. The tumor mass, epididymis and peritoneal pouch were removed en masse.

Pathology report: The oval encapsulated testis measured 10 cm. by 5 cm. and was composed of soft, gray, hemorrhagic, sarcomatous-appearing tissue without any normal architecture apparent. The attached cord-like structure showed several dilated and thrombosed veins. The essential lesion of the testis was a markedly anaplastic carcinoma of the embryonal type. The tumor cells in many instances appeared to practically line blood filled spaces within the substance of the tumor. The testicle had been almost completely replaced by tumor which had even invaded the epididymis. Diagnosis: Embryonal carcinoma of testicle (Dr. David A. Todd, San Antonio).

Postoperatively the patient was given deep roentgen therapy. Chest film done October 28, 1952 was normal. The patient has remained in good health to date.

Case 2. A. S., Mercy Hospital No. 6556, a 34 year old white man, was admitted October 26, 1950, because of a tender mass in the right groin of 2 to 3 months' duration which originally had been diagnosed as epididymitis of an undescended testicle. Under penicillin therapy the tenderness decreased, but the mass had shrunk only slightly in size. In addition dysuria, urinary burning and a small urinary stream were present. Gonorrhea occurred many years ago. In 8 years of married life, his wife had never become pregnant.

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On physical examination, the right testicle was present within the inguinal canal, was three times normal in size and acutely tender. The left testicle was not palpable. The external urethral meatus was small. A urethral stricture 5F in size was present one inch within the external meatus. The prostate was boggy. Urinalysis was normal. Complete blood count: Red blood cells 5,350,000, hemoglobin 14.2 gm., white blood cells 15,450; neutrophiles 79, lymphocytes 20, eosinophiles 1. Kahn test was negative. Chest film was normal.

A diagnosis of bilateral undescended testicles and possible right testicular tumor was made. A left inguinal incision was made, and a small, soft, flabby testis was found at the level of the internal ring. The cord was freed of adhesions, and sufficient length was obtained to place the testicle within the scrotum. A right inguinal incision was made. The cord was ligated and cut at the level of the internal ring, and the testicle removed. The urethral stricture was cut to size 30F following which a 28F sound could be passed with ease. A urethral catheter was left indwelling.

Pathology report: The testicle formed an oval, flattened mass measuring 9 by 7½ by 4 cm. There was a segment of vas deferens 6 cm. in length. The opened cut surface of the testis was found to contain a soft, necrotic, mottled, hemorrhagic tumor mass which measured 7 by 6 by 4 cm. The periphery was formed by the capsule and some fibrous thickening. The epididymis did not appear to be grossly involved and measured 3 by 1½ by 0.7 cm. The tumor of the testicle was a markedly anaplastic embryonal carcinoma which had practically destroyed all testicular tissue. The tumor was markedly necrotic in some areas with associated hemorrhage and what appeared to be infection. The epididymis was involved as was also the first portion of the spermatic cord. Diagnosis: Embryonal carcinoma of the testicle (Dr. David A. Todd).

Postoperative deep x-ray therapy was given. On March 19, 1951, the patient complained of hemoptysis, weakness, pain in the back of the head, and dizziness. Chest film showed a lesion 3 cm. in diameter in the second left anterior interspace. Additional deep x-ray therapy plus teropterin were given. The patient steadily declined and expired April 29, 1951. Permission for autopsy was not obtained.

Case 3. J. G., Mercy Hospital No. 7349, a 28 year old white man, was seen January 6, 1951, with the following history: Four days previously, while doing heavy lifting, the patient felt pain in the right testicle. That evening the pain became worse, and he had a low grade fever. A diagnosis of epididymitis was made, and penicillin given. Tenderness, however, persisted. In 1944 an operation had been done because of bilateral cryptorchidism. The right testicle had been brought into the scrotum; the left removed because of insufficient length of cord.

On physical examination well healed, bilateral inguinal scars were present. The right testicle was tender and slightly enlarged. It was thought that the epididymis was twice normal in size though a line of demarcation between testis and epididymis could not be felt. Urinalysis was normal. Complete blood count: Red blood cells 4,890,000, hemoglobin 13.5 gm., white blood cells 11,600; neutrophiles 75, lymphocytes 23, eosinophiles 2. Serology was negative.

A preoperative diagnosis of traumatic epididymitis was made. The scrotum was incised, and its contents evacuated. The testis was twice normal in size, bluish-black in color and quite hard. The epididymis was only slightly enlarged. The testicle was removed.

Pathology report: The specimen consisted of a markedly enlarged nodular testicle measuring 5 by 3 by 3 cm. The testicle was practically replaced by lobulated tumor of a solid structure and encephaloid appearance. Sections from the testicular tumor showed it to be typical embryonal type of carcinoma with heavy infiltration of stroma by lymphocytes. The tumor had practically replaced all of the testicular tissue although no serosal infiltration was seen. In areas the tumor has undergone marked necrotic changes. It had spread through into the epididymis which showed a right large tumor composed of embryonal cells. Diagnosis: Embryonal carcinoma of testicle involving epididymis (Dr. David A. Todd).

Postoperatively a course of deep x-ray therapy was given. Chest films have remained negative for metastasis, and the patient is in apparent good health.

DISCUSSION

Campbell states that failure of normal descent of the testicle occurs in 1 to 3 per cent of males. In 10 per cent of these it is bilateral. The proportion of abdominal to inguinal testes is 1:4. Descent usually takes place in the first year. If it has not done so by puberty, it is unlikely to occur.

A variety of pathological conditions are associated with cryptorchidism. More than 70 per cent have a concomitant inguinal hernia. Practically all postpubertal cryptorchid testes are sterile because of the heat factor (Moore). In addition atrophy due to interference with circulation, compression within the canal or to trauma may take place. Meyer reported 3 cases of fatal peritonitis due to suppurative epididymitis in abdominal testes.

Torsion of an intra-abdominal testicle is rare. Charendoff et al. found 19 cases in the literature and added one. Malignancy was present in 65 per cent of these.

Various authors have stated that the incidence of malignancy in cryptorchidism is 20 to 40 times as great as in normally descended testes. Moreover the chances of an abdominal testicle becoming malignant are greater than that of one retained within the inguinal canal. Whether all undescended testes are potentially malignant remains a controversial issue.

In 3½ years of private practice the author has seen 5 cases of malignancy of the testes. Three of the five were in undescended testes. One case of malignant degeneration took place 7 years after orchiopexy. Cabot believes that successful orchiopexy reduces the danger of malignant deterioration.

In view of the poor prognosis for undescended testes as to spermatogenesis, incidence of infection, trauma, and malignant degeneration, it behooves us to study this problem with care. In all probability undescended testes should be brought into the scrotum surgically at or before puberty if no response is obtained with hormone therapy. Testes which cannot be placed within the scrotum should be removed. It is suggested that surgical correction done some time after puberty does not reduce the possibility of malignant degeneration.

SUMMARY

Three cases of carcinoma in undescended testicles are reported. One was discovered concomitantly with torsion of an intra-abdominal testicle. Another occurred 7 years after orchiopexy.

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FATAL REACTION FOLLOWING AORTOGRAPHY WITH NEO-IOPAX

A. J. JOSSELSON AND JOSEPH H. KAPLAN

With the progressive refinement of injection techniques, administration of radio-opaque media has become a frequent diagnostic procedure. Because of increasing numbers of cases studied, toxic or allergic reactions may be encountered. To prevent repetition of serious or fatal reactions, as well as to assist in evaluation of new products, it becomes the duty of the physician promptly to report the occurrence of all untoward reactions. The product Neo-Iopax (Disodium N-methyl-3, 5-diiodo-chelidamate) has enjoyed a widespread acceptance in the field of excretory urography. Instances of allergic and other reactions to this material have appeared in scattered reports[1-8] in the literature. Reference[9] was made to a fatality resulting from the use of pyelectan in an editorial but the case was not described in detail. The following case is presented as an example of a fatal reaction to Neo-Iopax.

CASE REPORT

M. S., a 35 year old white woman, was first seen in May 1952 by one of us (A. J. J.) with the complaint of palpitation and headaches in early morning. She reported a systolic hypertension of 200 mm. of mercury known since September 19, 1951. She had been told during her pregnancy twelve years earlier that her blood pressure was elevated "slightly."

The blood pressure was 190 mm. of mercury systolic and 120 mm. diastolic. Examination of ocular fundi revealed moderate diffuse arteriolar sclerosis without exudates or hemorrhages. The optic discs appeared normal. No other physical findings of note were encountered.

Blood nonprotein nitrogen, complete blood count, serologic test for syphilis and electrocardiogram were negative or within normal limits. Roentgenogram of the chest was normal. Serum albumin was 3.6 gm. per 100 cc; serum globulin was 3.4 gm. Urinalyses revealed specific gravities of 1.008 and 1.009 with albuminuria ranging from trace to 2 plus. An excretory urogram made with 20 cc of a 50 per cent solution of Neo-Iopax revealed absence of visualization of the

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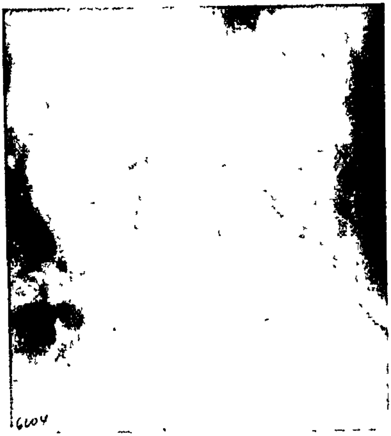

Fig. 1

left kidney with a large ureteral calculus measuring 1.2 cm. in diameter located at the ureterovesical juncture. There was a compensatory hypertrophy of the right kidney. Serum calcium and phosphorus were within normal limits and phenolsulphthalein excretion was 64 per cent in 2 hours.

Removal of the left kidney was contemplated because of its possible contribution to the vascular hypertension resulting from renal ischemia (Goldblatt effect). It was necessary to obtain an estimation of the circulatory status of the kidney before concluding that nephrectomy was indicated. Accordingly, on July 11 an aortogram was made through the translumbar approach. Neo-Iopax (15 cc of a 75 per cent solution) was used as a contrast medium. The procedure was performed with ease and the patient complained of no discomfort at the time. The renal arteriogram obtained is reproduced in figure 1. The day after this procedure the patient complained of nausea, vomiting, edema of the face and neck, and diffuse myalgic pains.

Because of protracted vomiting and a persisting ileus, the patient was hospitalized on July 16. The temperature was elevated to 100–101F during the first 3 days of hospitalization. Initial laboratory data revealed mild anemia and normal values for serum electrolytes. The blood nonprotein nitrogen was 120 mg. per cent. Bleeding time was reported as 21 minutes. The patient's symptoms persisted and the urine became grossly bloody; the volume averaged 200–500 cc daily. The oliguria persisted in spite of the administration of intravenous fluid in amounts calculated to replace fluid and electrolyte losses and to correct dehydration without producing edema. The hospital course was stormy and the patient did not respond to supportive therapy, which included blood transfusions, antibiotics and fluid and electrolyte replacement. The azotemia progressed with the blood nonprotein nitrogen stabilizing in the range of 580 mg.

per cent. The ileus was refractory to treatment. A terminal uremic pericarditis and diffuse petechial rash appeared and she died the twenty-sixth day.

At necropsy, the findings of note were confined to the lungs, heart and kidneys. Approximately 1500 cc of blood tinged fluid was present in the left pleural cavity and 1000 cc in the right cavity. The lungs weighed 800 gm. There was partial atelectasis of both lower lobes. The pericardial sac contained 500 cc of thin bloody fluid. A shaggy fibrinous red gray exudate was present on epicardial and pericardial surfaces.

The heart weighed 375 gm. Left ventricular hypertrophy was marked, the wall measuring 17 mm. in thickness. The endocardium was thin and smooth and there were no valvular defects. All major coronary arteries were patent and no significant atherosclerosis was observed.

The left kidney was a scarred, shrunken, nodular organ measuring 6 by 4 by 3 cm. Its slightly thickened capsule stripped with moderate difficulty leaving a pitted surface on which there was a solitary thin walled cyst 12 mm. in diameter. The sectioned surface revealed marked dilatation of the pelvis and all calyces. The entire parenchyma measured less than 5 mm. in thickness. At the left ure-

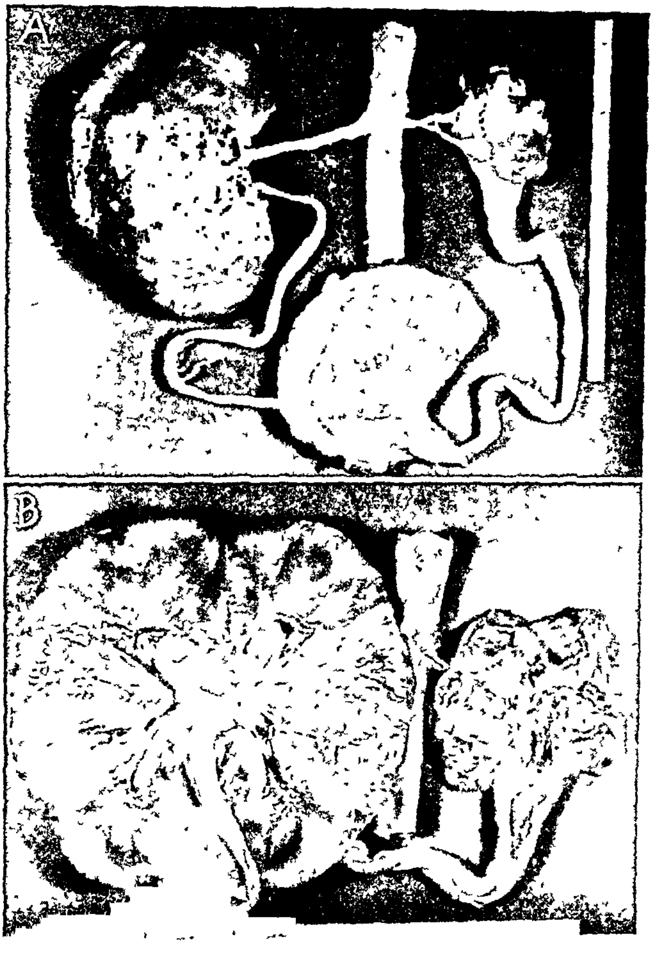

FIG. 2

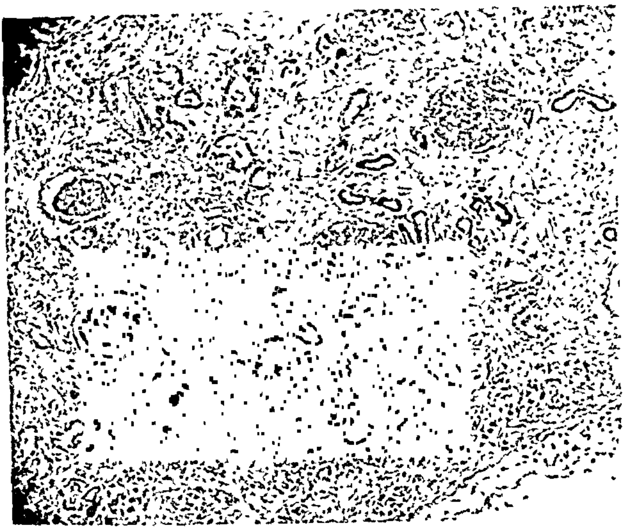

FIG. 3

terovesical juncture a dark brown stone measuring 1.2 by .8 cm. completely obstructed the ureteral ostium.

The right kidney extended nearly to the pelvic brim and measured 15 by 8 by 7 cm. A thin capsule stripped with ease leaving a soft, flabby, mottled, yellow-grey surface studded by soft, cortical abscesses measuring 1 to 3 mm. in diameter. Numerous pinpoint areas of hemorrhage were also observed scattered over the cortical surface. Similar hemorrhagic areas also were seen in the sectioned surface throughout the cortex and miliary abscesses up to 1 cm. in diameter were found in the medullary portions and tips of the pyramids. The ureter appeared normal. The kidneys and bladder are reproduced in figure 2.

Microscopic sections of the left kidney revealed findings consistent with advanced stage of severe chronic pyelonephritis. Findings in the right kidney are represented in figure 3. Several distinct processes were apparent as represented by multiple small abscesses, intimal fibrosis involving arterioles and small arteries, infarction of glomeruli with hemorrhage into the capsular spaces, and various stages of tubular destruction and regeneration. In many of the proximal convoluted tubules there were marked destruction and desquamation of lining epithelium. Regenerating flat, darkly staining, newly formed epithelial cells were seen in numerous tubules.

COMMENT

This is a case of hypertensive cardiovascular disease associated with an atrophic left kidney secondary to chronic hydronephrosis and pyelonephritis. In spite of a diffuse nephrosclerosis the contralateral kidney exhibited only moderate impairment of function until a severe insult precipitated renal failure. Clinically this reaction followed and was apparently produced by an aortogram in which Neo-Iopax was used. Because of facial edema, prolonged bleeding time, and severe gastro-intestinal disturbance, it was presumed that the episode was produced by an allergic response to the dye. However, the anatomical changes found in the glomeruli and tubules of the right kidney suggested a severe toxic reaction, such as that which may be seen with acute heavy metal poisoning. It is true that a high concentration of the dye probably entered the right kidney, as revealed by the roentgenogram. This may be attributed to the absence of circulation in the left kidney and perhaps also to the fortuitous placement of the needle in the aorta exactly opposite the lumen of the right renal artery. This however, was the purpose of the procedure technically and should not pose an undue hazard for the patient or a penalty for the physician.

Though there were advanced vascular changes in the right kidney, this patient might still have enjoyed a favorable response following a left nephrectomy. Instead a fatal reaction following the use of Neo-Iopax occurred.

SUMMARY

An aortogram, in which Neo-Iopax was used, apparently produced a toxic reaction which was fatal to a patient with hypertensive cardiovascular disease associated with one atrophic kidney. Reports indicate that nonfatal untoward reactions to Neo-Iopax are not uncommon. This case is presented to indicate this dye may also be lethal in its effects.

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THE CLINICAL USE OF CYCLAINE (HEXYLCAINE) AS AN ANESTHETIC AGENT IN UROLOGICAL SURGERY:—A REPORT OF OBSERVATIONS OF 1000 PATIENTS

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Hexylcaine (1-cyclohexylamino-2-propylbenzoate) was synthesized by Hancock, et al. 1944.[1] Its possible clinical use was suggested by animal studies conducted by Beyer, et al. 1948.[2] They showed the compound to have an order of toxicity comparable to procaine, an order of topical anesthesia comparable to cocaine, an order of nerve block anesthesia intermediate between butacaine and tetracaine, and a duration of spinal anesthesia second only to tetracaine (over twice as long as procaine).

There followed a preliminary clinical report of its usefulness by Ruben and Anderson 1949[3] who observed 400 patients in whom cyclaine anesthesia was used. They concluded, "our experience to date indicates that the new drug provides complete and longer lasting nerve block in smaller doses relative to its animal toxicity than does procaine." Torkelson and Cooley 1951[4] reported on its use in low spinal anesthesia in obstetrics in 1000 patients. They were impressed by the uniformly satisfactory anesthesia obtained and "the large percentage of patients in whom there was no appreciable lowering of blood pressure." According to Orkin and Rovenstine 1952,[5] cyclaine in 1 per cent solution is stable to boiling and autoclaving for sterilization purposes. The solution is stable for one or more months with no apparent loss of effectiveness.

Our observations were begun July 1952 and continued for one year. During this time cyclaine anesthesia in one form or another was given to 1000 patients. Types of anesthetic techniques and numbers of patients involved are presented in table 1.

CYCLAINE FOR CAUDAL ANESTHESIA (320 PATIENTS)

A solution of cyclaine in the concentration of ½ of 1 per cent was used for all caudal anesthesias. The dosage was 30 to 40 cc. In figure 1 the technique of single dose caudal anesthesia is illustrated. Figure 2 shows an actual dissection of the caudal canal with relationship of the caudal needle to the cauda equina

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Sharp and Dohme, Inc., Philadelphia, Pa. furnished cyclaine (hexylcaine) for this investigation.

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TABLE 1. *Types of cyclaine anesthetic techniques*

	NUMBER OF PATIENTS
Caudal	320
Continuous caudal	75
Hyperbaric spinal	140
Hypobaric spinal	25
Topical: female bladder and urethra	75
Topical: male urethra	225
Local infiltration	140

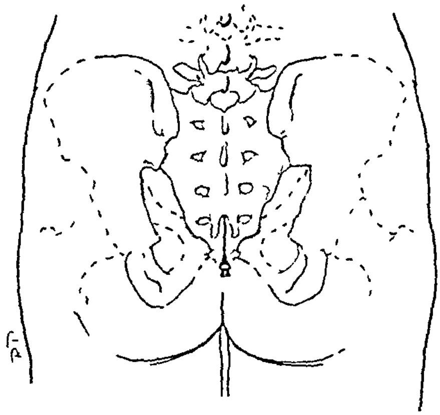

FIG. 1

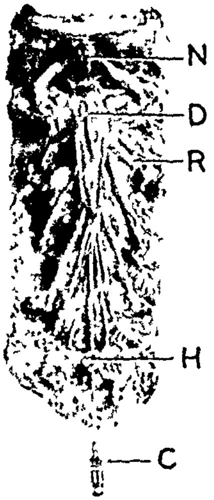

FIG. 2

FIG. 1. Schematic anatomical presentation of technique of single dose caudal anesthesia; No 19 needle in caudal canal.

FIG. 2. Photograph of actual dissection of caudal canal showing in detail: *N*, spinal cord; *D*, dura; *R*, nerve; *H*, hiatus of caudal canal; *C*, No. 19 caudal needle.

In table 2 the various procedures done under single dose caudal anesthesia are enumerated.

In this series of 320 single dose caudal anesthesias surgical anesthesia was obtained in 3 to 7 minutes and remained profound for the duration of the procedure. No supplemental anesthesia was necessary. There were no untoward reactions.

CYCLAINE FOR CONTINUOUS CAUDAL ANESTHESIA (75 PATIENTS)

A solution of cyclaine in the concentration of ½ of 1 per cent was used for all continuous caudal anesthesias. The initial dose was 80 cc, supplementing as needed during the course of the surgery. Only five of the patients required any supplemental administration of the agent. In figure 3 the technique of continuous caudal anesthesia is illustrated. In table 3 the procedures done under continuous caudal anesthesia are enumerated.

Anesthesia was profound and satisfactory for the duration of the procedure

TABLE 2. *Procedures done under single dose cyclaine caudal anesthesia*

	NUMBER OF PATIENTS
Cystoscopy, ureteral catheterization and retrograde pyelography	231
Cystoscopy	70
Transurethral resection of prostate	3
Circumcision	3
Ureteral dilatation	2
Internal urethrotomy	2
Transurethral fulguration	2
Urethral dilatation	2
Litholapaxy	1
Meatotomy	1

in every patient. One patient had a mild transient loss of consciousness shortly after injection of the cyclaine solution, but recovered in about 5 minutes.

CYCLAINE FOR HYPERBARIC SPINAL ANESTHESIA (140 PATIENTS)

A solution of cyclaine in the concentration of 1 per cent in 5 per cent dextrose was used for all "low spinals." Four to five cubic centimeters of the solution (40 to 50 mg. of cyclaine) were used. The specific gravity of this hyperbaric solution was found to be 1.0200 (spinal fluid is 1.0060). In table 4 the procedures done under this method of "low spinal" are enumerated. In all instances the solution was injected intrathecally without dilution with spinal fluid, the pa-

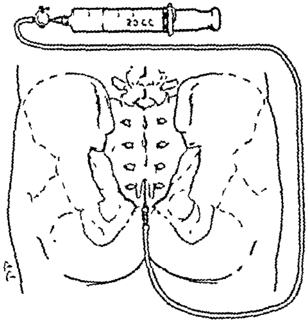

FIG. 3. Schematic anatomical presentation illustrating technique of continuous caudal anesthesia. No. 19 malleable steel needle in caudal canal and connected to supply of ½ of 1 per cent cyclaine solution in syringe.

TABLE 3. *Procedures done under continuous caudal anesthesia using cyclaine*

	NUMBER OF PATIENTS
Perineal prostatectomy	72
Total radical prostatoseminalvesiculectomy	3

TABLE 4. *Procedures done under hyperbaric spinal cyclaine*

	NUMBER OF PATIENTS
Transurethral resection of prostate	74
Transurethral fulguration of bladder tumor	24
Cystoscopic manipulation for ureteral calculus	15
Cystoscopic examination with retrograde pyelography	4
Litholapaxy	4
Cystoscopy	4
Internal urethrotomy	4
Excision urethral lesions	4
Meatotomy	2
Orchidectomy	2
Transurethral endovesical ureterolithotomy	1
Circumscision	1
Excision of spermatocele	1

tient being in sitting position during injection and for three minutes following injection.

In all instances the anesthesia was rapid in onset (3 to 5 minutes), profound, and of a duration sufficient for the operative procedure. No supplemental anesthesia was necessary and there were no untoward effects.

CYCLAINE FOR HYPOBARIC SPINAL ANESTHESIA (25 PATIENTS)

A solution of cyclaine in the concentration of ¼ of 1 per cent was used for all hypobaric spinal anesthesias. This solution was prepared by diluting 1 cc of 5 per cent cyclaine with sterile distilled water to a volume of 20 cc. The hypobaric solution thus prepared contains 2.5 mg. of cyclaine per 1 cc and has a specific gravity of 1.0028 (spinal fluid is 1.0060). The solution is injected intrathecally without dilution with spinal fluid with the patient in lumbar position, operative side up. We have preferred to inject through a Lemmon continuous spinal setup; in the event that the operation is prolonged, supplemental injections may be given. The dosage is 10 to 15 cc (25 to 37.5 mg). The technique is shown in figure 4. Anesthesia developed in 3 to 7 minutes after initial injection and was profound allowing completion of the surgical procedures without supplemental injection of solution. No untoward reactions occurred.

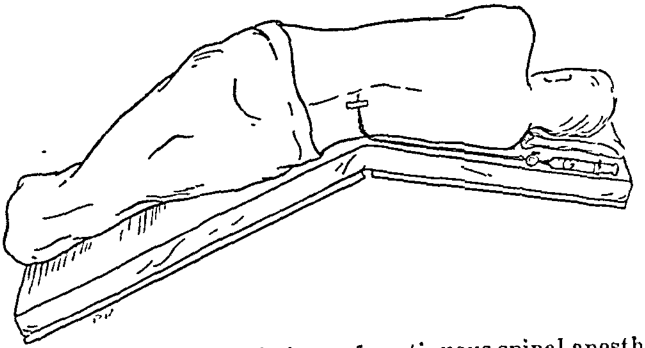

FIG. 4. Schematic presentation of technique of continuous spinal anesthesia using hypobaric cyclaine solution for lumbar surgical approach.

TABLE 5. *Procedures done under hypobaric spinal cyclaine*

	NUMBER OF PATIENTS
Nephrectomy	16
Ureterolithotomy	4
Pelvioplasty	2
Nephropexy	1
Pelviolithotomy	1
Nephrostomy	1

TOPICAL CYCLAINE ANESTHESIA OF THE FEMALE BLADDER (75 PATIENTS)

A solution of cyclaine in the concentration of 1 per cent was used for all topical cyclaine anesthesias of the female bladder. The bladder was drained with a small urethral catheter and 30 cc of the solution introduced. In table 6 the procedures done under this type of anesthesia are enumerated.

Anesthesia was almost immediate in onset and satisfactory for completion of the procedure. There were no untoward effects.

TABLE 6 *Procedures done under topical cyclaine anesthesia in the female*

	NUMBER OF PATIENTS
Cystoscopy, ureteral catheterization, and retrograde pyelography	68
Cystoscopy	7

TOPICAL CYCLAINE ANESTHESIA OF THE MALE URETHRA (225 PATIENTS)

A solution of cyclaine in the concentration of 5 per cent was used for all topical cyclaine anesthesias of the male urethra. Five cubic centimeters of the solution were introduced into the urethra with the 5 cc urethral tip glass Asepto syringe. The solution was retained in the urethra by finger pressure for a period of 3 minutes before beginning instrumentation. In table 7 the procedures done under this type of anesthesia are enumerated.

TABLE 7. *Procedures done under topical cyclaine anesthesia in the male*

	NUMBER OF PATIENTS
Cystoscopy	205
Urethral dilatation	20

TABLE 8 *Procedures done under local infiltration anesthesia with cyclaine*

	CC OF ½ OF 1% CYCLAINE	NUMBER OF PATIENTS
Bilateral vasectomy	5 cc each side	124
Circumcision	50 cc	4
Bilateral orchiectomy	30 cc each side	5
Suprapubic cystostomy	100–150 cc	3
Biopsy scrotal lesions	10–20 cc	2
Meatotomy	5 cc	2

Anesthesia was almost immediate in onset and satisfactory for completion of the procedure. There were no untoward effects.

LOCAL INFILTRATION ANESTHESIA WITH CYCLAINE (140 PATIENTS)

A solution of cyclaine in the concentration of ½ of 1 per cent was used for all local infiltration anesthesias. The amounts used in any one patient varied from 5 to 150 cc of solution. In table 8 the procedures done under this type of anesthesia are listed.

Experience with cyclaine as an agent for infiltration anesthesia impresses one with its almost immediate onset, excellent spreading factor, and depth of anesthesia. There were no serious immediate or delayed systemic reactions, or evidence of any acute or delayed local tissue damage or irritation.

SUMMARY

Cyclaine is an anesthetic agent with qualities suitable for use in infiltration, regional, and topical anesthesia. It possesses the advantages of rapid onset, prolonged activity, profound depth of anesthesia, and decreased toxicity.

It would appear clinically that cyclaine is less toxic than procaine and that cyclaine is a more satisfactory topical anesthetic agent in the bladder or urethra than 2 per cent cocaine.

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A NEW INTERCHANGEABLE TUMOR RESECTING INSTRUMENT

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Neoplasms of the bladder have received intense therapeutic attention by all urologists in an effort to evolve the best surgical approach. Those who advocated the most radical surgical attack on all but the simple papillomas have had their opportunity to present their results. Likewise, the time honored results of destruction of papillary neoplasms of varying malignancy by physical agents have been impressed on urological thinking. The author, like all urologists, has considered his own experience and the published results of the great clinics.

Cystoscopic experience and acumen helped by biopsy must still be the greatest factor in choice of procedure. Surface malignancies which are papillary in type can be treated successfully and some permanently cured by physical modalities. Infiltrative papillary and nonpapillary lesions (neoplastic extension deeply into and beyond the muscularis) can not be cured by physical agents and few can be cured by the most radical surgical approach. However, partial and very radical cystectomy unquestionably have a definite place in the therapy of bladder neoplasm.

In 1936 the author presented a ball tipped interchangeable electrode to be used with a McCarthy electrotome and at that time predicted that the resectoscope was the most natural and precise instrument for the instrumental treatment of bladder neoplasm. His thought at the time was that a ball tipped electrode used at the base of a growth gave deep penetration of electrocoagulation where it was most needed. As the era of bold resection of the prostate advanced it was inevitable that bold electroresection of growths should have its trial. Extensive experience has demonstrated that electroresection of the mass of the growth is best and deep electrocoagulation of the base of the growth is desirable. Parallel clinical and pathological studies of excised neoplastic bladders revealed the limitation of both the physical and surgical treatments and may have served to stabilize urological thinking.

During instrumental resection of papillomatous growths, some of rather broad base, the loop of the resectoscope has sometimes failed to cut growths which were not fixed since the villi floated away from the loop. The author therefore presented to Mr. Frederick J. Wallace the idea which is hereafter described. If the instrument is worthy of gathering momentum it will be due to the genius and kind interest of a person who has already earned the most honored and revered regard of urologists everywhere.

Figure 1 reveals an interchangeable element which can be passed through a No. 28 resectoscope sheath. A spring maintains the cutting loop in the proximal position well inside the No. 28 sheath. Visualization is obtained with a No. 68 McCarthy panendoscopic telescope. Thumb pressure forward pushes the loop retrograde from the inside of the resectoscope sheath distally through the newly formed fenestra into the terminal recessed beak. Release of thumb pressure

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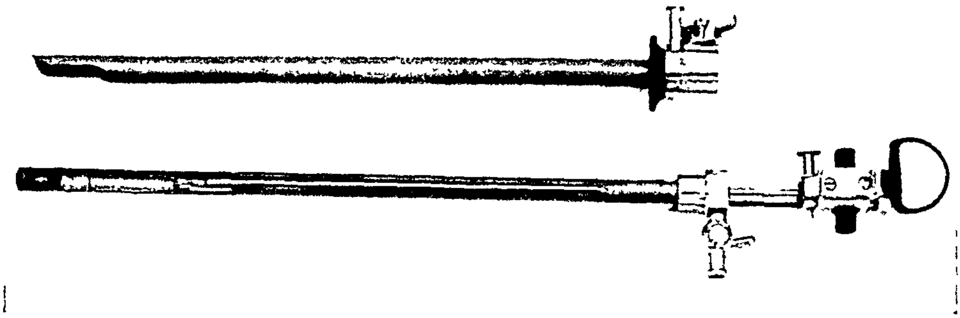

FIG. 1

permits the loop to be returned to its original position within the sheath. Thus tissue fixed between the loop moving retrograde and the terminal hollow, niched beak can be cut and if desired the loop returning to its original position may be activated by the cutting current for the purpose of resection.

The field of usefulness for such an interchangeable element should be greatest for certain types of neoplasms and also for retrograde resection of residual prostatic tissue close to the external sphincter during endoscopic resection of the prostate. In the latter instance the external sphincter may be protected from accidental injury.

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RENAL PAIN

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It is the purpose of this presentation to call further attention to a group of patients who complain of pain typical of that usually associated with disease of the kidneys and ureters without demonstrable pathological changes. Renal and ureteral pain is usually associated with obstructive lesions of the upper urinary tract, and one can usually demonstrate a stone, a stricture, stenosis of the ureteral orifice, a kink in the ureter, or ureteropelvic obstruction. Renal pain may also be associated with perirenal inflammation in tumors of the kidney, particularly when hemorrhage has occurred within the tumor, and with renal cysts.

We are occasionally consulted by patients who present none of these pathological processes, whose kidneys appear normal in outline, whose pelves and ureters have a configuration within normal limits, and in which function and emptying time is normal. Yet, the patient complains of constant or periodic pain that cannot be differentiated from the pain we commonly associate with demonstrable renal disease. These patients are usually women and the pain has its onset during the menstrual time of life. In most cases the patients are of a highly nervous temperament and in many instances such factors as economic insecurity, domestic or personal affairs further complicate the problem. The marital state does not seem to be significant. Of 8 patients reported by Crabtree, four were married. Young et al. reported 5 cases of nephralgia, two of whom were married, and of the four patients recorded in this report only one was single. In most cases the patient bears from one to several abdominal scars, the result of surgical efforts to restore her health.

In many instances the onset of pain follows rather closely some previous illness usually involving the kidneys or pelvic structures. One of my patients first suffered pyelonephritis following a pelvic operation. Two had been operated upon for renal ptosis and one had had bilateral renal calculi with the loss of one kidney. Delayed emptying of the renal pelvis without evidence of organic obstruction is occasionally encountered, and minor degrees of renal mobility are not unusual. In some cases the ureterogram presents a straight, narrow tube as evidence of ureteral spasticity.

L. S. Young, W. E. Wilson and R. Nelson in the *Journal of Urology* (May 1950) in a discussion of nephralgia present an excellent description of the autonomic nervous system as related to renal pain. A brief abstract of this discussion is herewith presented. It is generally agreed that the nerve supply of the kidney is derived solely from the autonomic nervous system, and is both sympathetic and parasympathetic. Parasympathetic fibers from the vagus nerve pass to the kidney by way of the celiac and aortic plexuses. The function of the parasympathetic nerves is not understood. The sympathetic nerve supply is mainly from the celiac ganglion and aortic plexus. Preganglionic fibers are received from the sixth thoracic through the first lumbar sympathetic ganglia, by way of the greater, lesser and least splenic nerves. A fine network of post ganglionic fibers surround the renal artery and its branches. Fibers also travel within the muscular

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coat of the blood vessels. It is therefore evident that denervation of the renal vessels cannot be completely effective. Sympathetic nerves terminate within the smooth muscle tissue of the renal tubules and calyces. There are both efferent and afferent fibers. The efferent fibers are thought to cause constriction of the muscle cells and also vasodilation. Painful sensations arising in the kidney and ureter pass over the afferent nerve. The preganglionic fibers of the sympathetic system pass in the intermediolateral columns of the cord. There is evidence that there is cortical representation in the autonomic system in the premotor cortex of the frontal lobes. Following prefrontal lobotomy in the treatment of severe nervous disease, many disagreeable effects of a disturbed autonomic system have been relieved or ameliorated. It has therefore been suggested that patients suffering from nephralgia who have been classified as emotionally unstable, may have emotional instability which relieves itself by an overflow into the autonomic nervous system rather than by personal adjustment.

Maier, Engelmann, Wharton and others believe that the ureters can function automatically and initiate their own muscular contraction without the necessity of external neural connection. Barringer, Wu and Quinby are agreed that adequate stimulus for ureteral peristalsis is diuresis. Lapides demonstrated that ureteral peristalsis will continue despite interference with nerve supply to the ureters. He therefore believes that the ureter is an autonomous organ and that the autonomic ganglion takes no part in maintaining ureteral contraction. Caldwell, Marks and Rowntree denervated the renal pedicles of a group of dogs upon which subsequent renal studies were done. There was no change in the excretion of dyes. Concentrative powers of the kidneys were temporarily diminished. This persisted in one dog for two months. After five months, the only evidence of change in function was increased diuresis.

In 1921, Papin and Ambard advocated renal sympathectomy for the relief of renal pain associated with small hydronephrosis. They reported relief in four of six patients. Function tests reveal no difference in the function of the kidney following operation. There was no change in the hydronephrosis. A nephropexy and renal decapsulation was done on these patients. Therefore it is difficult to evaluate the results.

In 1943, Elmer Hess discussed renal denervation and mentioned the fact that the operation had been advocated for the relief of reflex anuria, nonmechanical hydronephrosis, early tuberculosis, prevention of renal calculi, hypertension and nephralgia. There was no evidence that the operation had been helpful in any but the latter.

In 1948, Granville Crabtree reported 8 patients upon whom renal denervation had been done. There was complete relief in five. In one there was a complete failure. One patient was probably relieved for two years and another for three years. He called attention to the fact that most patients with unexplained renal pain were of a highly nervous temperment and that neurosis had been diagnosed in almost all instances.

Elwood Young and associates were of the opinion that patients in this group should include those with abdominal or back pain of proven renal or ureteral origin in whom no obvious causes can be found, including those cases of minimal hydronephrosis for which no organic explanation can be found. They state that it has been shown that an autonomic reflex arch exists which is similar to the somatic arch and it is felt that an inbalance of the autonomic nervous system is a common cause of renal pain without demonstrable organic changes. Young suggested that following a complete physical examination and urological study, certain tests should be carried out to determine whether or not renal denervation might be expected to be of benefit. First, the administration of Etamon, with the idea of blocking the autonomic nerves. Second, administration of a placebo in the place of Etamon. The patients getting relief from the placebo should be treated on a psychotic basis. Third, unilateral paravertebral splenic chain and dorsal lumbar sympathetic ganglion block from D9 to L2 during an attack of pain. The patient whose symptoms are relieved by a sympathetic block, either by the use of novacain or by the use of Etamon, should respond to adequate denervation. Young reported five patients, one cured by nephrectomy, one relieved by frequent ureteral dilatations, one apparently relieved by ureteral dilatations and sympathetic block, one cured by sympathectomy, and one partly relieved by Etamon, placebos, parasympathetic excision refused.

I present 4 patients, all of whom have had previous operations for the relief of renal pain. Two are relieved by sympathectomy and one by a cordotomy. These three patients were practically invalids because of discomfort and at the present time are carrying on their normal household or business duties. The fourth patient has been relieved of pain in the left renal and ureteral areas. Since the sympathectomy was done she has been operated upon because of a herniated disk. At present she complains of pain in the right lumbar area. This pain is not constant, but quite severe at times. Because of the diagnosis of herniated disk shortly following the sympathectomy, the advisability of the operation has been questioned. The patient however is positive that she obtained definite relief from the sympathectomy. The operation in this case is not recorded as a complete success.

CASE REPORTS

Mrs. A. B., aged 34, was admitted to St. Elizabeth's Hospital November 30, 1950 because of pain in the right costovertebral area and in the lower part of her abdomen. The pain was of 6 years' duration but had gradually grown worse until she was practically incapacitated. In 1947 her right kidney was suspended without appreciable relief. Examination showed her kidney to be in good position. There was a slight angulation of the right ureter near the renal pelvis. The only other evidence of a pathological process was spasticity of the colon. She was treated 3 months with bed rest, ureteral dilatations, antispasmodics and placebos without improvement. March 14, 1951, a thoracolumbar sympathectomy was done and because of the angulation of the right ureter the kidney was exposed and freed of adhesions. An aberrant blood vessel at the lower pole was ligated and divided and all nerve trunks that could be identified were stripped from the renal artery. The kidney was fixed in a normal position.

Convalescence was uneventful. Twelve months following the sympathectomy she reported that she was in better health than she had been for several years and had required no medical attention since leaving the hospital.

Miss E. H., aged 33, was admitted to St. Elizabeth's Hospital November 18, 1950 because of pain in the left costovertebral area, radiating into the lower abdomen and left leg. She stated that she had had pain in her back or abdomen almost constantly since she was a child. Her history disclosed numerous hospital admissions. Her appendix was removed when she was 17 years old. A year later a partial excision of the right ovary and a presacral nerve resection was done. At that time a diagnosis of right ureteral stricture was made. Three years later, her right kidney was removed because of hydronephrosis and stone. Six years later, she had a left nephrolithotomy and at the age of 31, a cholecystectomy. Examination showed a poorly nourished but well developed young woman complaining of constant left costovertebral pain which varied in intensity. The pain frequently radiated into the lower abdomen and left leg. There was good function from the remaining kidney. There was no evidence of ureteral obstruction nor was there any dilatation of the renal pelvis. A small stone occupied the terminal portion of an upper calyx. After considerable deliberation, I decided to attempt denervation of the left kidney. The operation was extremely difficult. The kidney was larger than normal, densely adherent and could not be delivered into the wound without undue risk. The small stone could not be located. The capsule was stripped from the kidney and the wound closed.

She felt better for about a month, and then returned complaining of the same pain except more localized. She was then seen by two surgeons who after obtaining psychiatric consultation refused to do a lumbar sympathectomy. I was not convinced that the pain was on a psychoneurotic basis and advised that she consult a neurosurgeon in a near by city. He elected to do a cordotomy. Since this operation 2 years ago she has been employed regularly as a secretary and has not required medication for pain.

Mrs. B., a woman aged 35, was first seen August 4, 1952 because of pain in the left costovertebral area radiating to the lower abdomen. In August 1951 she had a right nephropexy and the left kidney had been suspended five months later. The patient stated that there had been no relief of pain on the left side following the operation. She gave a history of passing blood when the pain was severe. The urine contained blood in microscopic amounts. Her pain was to some extent relieved by Etamon but the side effects were such that she refused to take it.

After approximately 30 days' treatment with ureteral dilatations, antispasmodics and sedatives, a sympathectomy was done, removing the ganglia from the tenth dorsal to the first thoracic inclusive. The patient was not immediately relieved of pain but has gradually improved until at the present time there is no discomfort on the left side. One month following the operation she was again admitted to the hospital because of pain in the lower part of her back radiating into her left leg. In November she was operated upon for a protruded disk at the fourth interspace. This somewhat confuses the picture but it is doubtful that the herniated disk caused pain in the lumbar area. At the present time she has no left lumbar pain but has frequent attacks of pain on the right side of the abdomen.

Mrs. L. H., aged 41, was admitted to the Hospital Division of the Medical College of Virginia June 9, 1944 because of pain in the right lower quadrant of the abdomen and uterine bleeding A perineal repair and a hysterectomy were done Pathological diagnosis: myomas of the uterus Inability to void required catheterization over a prolonged period The patient had pyuria, chills and fever which gradually responded to ureteral catheter drainage Because of persistent pain, an excretory urogram was made and showed moderate bilateral renal ptosis

She was re admitted to the hospital 4 months later because of pyuria and pain in the left side of the abdomen There was tenderness and general discomfort in both costovertebral areas Both ureters were dilated to 12F There was temporary relief of pain but during the next three years she had repeated cystoscopic treatments and was given every available antispasmodic and pain relieving drug

Four years following her first admission, because of persistent bilateral flank pain exaggerated upon exertion and pyelectasis, bilateral nephropexy was done Following this procedure she was entirely relieved of pain for 2 years

April 1, 1951, twenty-eight months following nephropexy, she was again admitted to the hospital because of pain in the right flank and right lower quadrant of the abdomen During the summer the right ureter was dilated several times and the patient required medication for pain almost constantly At no time had there been any return of pain on the left side November 11, 1951 she was again admitted to the hospital and a sympathectomy was done on the right side, removing the sympathetic chain and ganglia from D10 to L2 Also the greater and lesser splanchnic nerves from the D10 level to the celiac ganglion were removed There was moderate discomfort in the right lumbar area and abdomen for three or four weeks after which she expressed herself as feeling quite well She has not required medical attention since the sympathectomy was done

Pain of renal and ureteral origin is not unusual without objective evidence of renal and ureteral disease Such pain is probably caused by some disturbance of sympathetic nerve supply The condition is usually spoken of as nephralgia After thorough investigation has failed to discover a pathologic process to account for the pain, a correct diagnosis can usually be made by blocking the nerve supply to the kidney with novacain or by the administration of Etamon to produce an autonomic blockade In many of these patients there is a decided psychic element which must be taken into account but the psychiatrist alone is rarely, if ever, successful in relieving the pain Division of the autonomic nerve supply to the kidney either by renal pedicle denervation or by lumbar sympathectomy does not endanger the functional capacity of the kidney

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PATHOGENESIS OF RENAL FAILURE

JOHN T. MACLEAN

We are concerned primarily with the mode of development of the lesion in the kidney which leads to the production of acute renal failure. It is presumed that the pre-renal causes of failure such as a diminished fluid intake, a reduction in the constituents of the blood as occurs in haemorrhage, diarrhoea and vomiting have been excluded. Likewise it is presumed that the post-renal factors which cause obstruction to the outflow of urine have also been excluded.

This process of elimination narrows our problem down to the specific problem of what is occurring in the intrinsic renal lesion, and what are the contributing factors in its production. Figure 1 represents a diagrammatic concept of the various contributing factors which will be discussed in more detail subsequently.

A. GLOMERULONEPHRITIS

Figure 2 shows a normal glomerulus. It is not difficult to visualize that in an acute inflammatory reaction the polymorphs rush to the scene of action, so that very soon the entire glomerulus becomes a seething congested mass of inflammatory cells (fig. 3). In addition, Bowman's capsule becomes filled with an inflammatory exudate. Likewise, it is not difficult to conceive that if a sufficient number of units are so involved and their function eliminated, that acute renal failure may ensue. Clinically, we are well able to recognize this type of lesion with the sudden onset of mahogany coloured urine, hypertension, marked albuminuria, many red blood cells and white blood cells in the urine, and granular casts, followed in a few days, in some cases, by anuria.

Sulfonamide anuria. Sulfonamide anuria should be mentioned and excluded. Its mode of onset may vary considerably. There are four types of lesion possible: 1) Seventy-five per cent are due to mechanical blockage of the ureters by mixed blood clot and crystals. We have had 3 cases of sulfonamide anuria admitted within the past month. All three were due to sulfamerazine. All three had mechanical obstruction of the ureters with blood clot and crystals. All three promptly recovered when the ureters were catheterized and the pelves washed out. The lesion may be 2) toxic glomerulonephritis, 3) focal necrosis, or 4) a lower nephron-nephrosis type of lesion with disruption of the tubule at several points along its course.

Bilateral diffuse cortical necrosis should also be excluded. This lesion is defined by Duff and Moore as a pathological entity of unknown cause manifested by extensive uniform necrosis of the cortex of both kidneys. There are two theories of origin: 1) that it is due to toxins, as in pregnancy; 2) that it is due to ischaemia causing vascular occlusions. Clinically there is oliguria, anuria, and pain, usually epigastric, radiating along the ureters. Edema of the dependent parts occurs. The outcome is usually fatal; however, a very few patients do recover.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

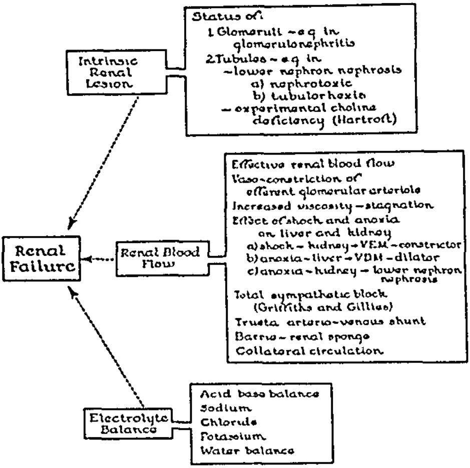

Status of
1. Glomeruli – eg in glomerulonephritis
2. Tubules – eg in
– lower nephron nephrosis
a) nephrotoxic
b) tubulorhexis
– experimental choline deficiency (Hartroft)
Intrinsic Renal Lesion
Effective renal blood flow
Vaso-constriction of efferent glomerular arteriole
Increased viscosity – stagnation
Effect of shock and anoxia on liver and kidney
a) shock – kidney → VEM – constrictor
b) anoxia – liver → VDM – dilator
c) anoxia – kidney – lower nephron nephrosis
Total sympathetic block (Griffiths and Gillies)
Trueta arterio-venous shunt
Barrie – renal sponge
Collateral circulation
Renal Failure
Renal Blood Flow
Electrolyte Balance
Acid base balance
Sodium
Chloride
Potassium
Water balance

FIG. 1. Diagram indicating main contributing factors in production of anuria

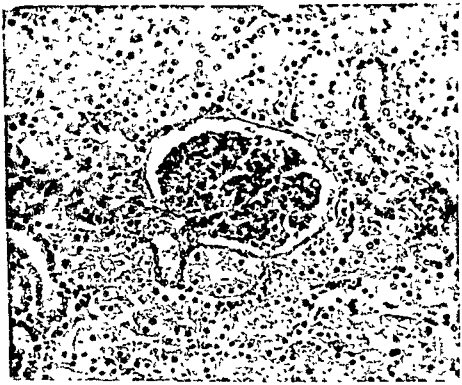


FIG. 2. Normal renal glomerulus showing afferent arteriole

B. TUBULES

A considerable amount of interest has centered around the lesion in the tubules. The exact sequence of events leading up to the production of "lower nephron nephrosis" still remains a matter of conjecture.

Lucké in 1946 gave an excellent description of the microscopic lesion, as being one of edema of the cells lining the distal convoluted tubules, followed by degeneration and necrosis of these cells. Numerous haem casts are also present. These are made up of myohaemoglobin and haemoglobin. There are two views held regarding the appearance of haem casts in the tubules. One is that haemo-

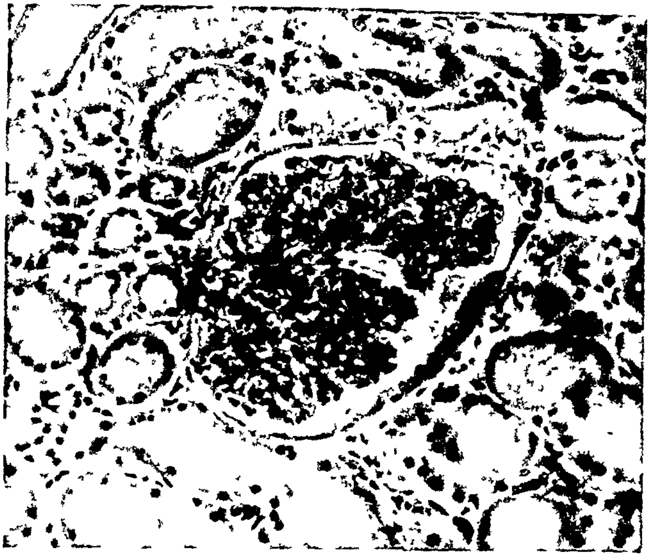


FIG. 3. Renal glomerulus in acute glomerulonephritis. Note inflammatory cells in glomerular tuft and protein exudate in Bowman's capsule.

globin may dissociate into molecules of smaller size and pass through the glomerulus, whereas myohaemoglobin is allowed to pass because of the increased permeability of the glomerulus. The other view is that these two compounds settle out in situ, from the debris locally present.

Much of the current work on this problem is divided into two phases: a) original investigation; b) a determined effort to eradicate the name and substitute another which renders the concept of pathogenesis even more opaque.

There are many names in medicine that are in their true sense misnomers, and yet have survived the years. The main objection to the name "lower nephron nephrosis" is that the lesion is not limited to the lower nephron, and that it is not a nephrosis but a nephritis. These seem like legitimate objections. However, if one concedes all this, it would still appear to be a reasonably good name.

Oliver et al. in 1951 reported on his investigations following the study of cases in which the individual nephrons were dissected out and studied. He believes that there are two types of lesion which may occur: A) Nephrotoxic damage. This occurs for example in mercury poisoning. The lesion is present only in the proximal convolutions, and is evenly distributed amongst all the nephrons. Debris may be packed within the lumen of the tubule, but the basement membrane remains intact. At the commencement there is a hydrops of the tubular cells followed by flattening of the epithelial cells, and death of the cells.

b) Tubulorhexis. Here there is disintegration of the tubular membrane, the epithelial cells become necrotic. This may involve only a portion of the wall of a tubule, or the whole wall may be involved resulting in loss of continuity. The lumen of the tubule thus lies open to the surrounding interstitial tissue. The interstitial reaction may be nil or it may be extreme. There may be masses of connective tissue fibres surrounding the tubule, or the surrounding reaction may be granulation tissue. This type of lesion is found in every segment of the nephron, but is most common in the terminal portion of the proximal convolution where it dips into the medulla, and in the distal convolution and connecting tubule.

What occurs next? In the portion of the tubule involved with the nephrotoxic edema and death of the cells, regeneration of the cells occurs, but function is not necessarily restored. In the tubulorhexis type of lesion, if there is some continuity of the tubule, regeneration may occur; whereas if the tubule is completely divided, it may never unite, or the ends may be invaded and obstructed by growing granulation tissue extending from the interstitial tissue.

One may reasonably question the isolationism of this theory of nephrotoxic damage. It is assumed that most toxins are more concentrated in the proximal tubule than elsewhere, and that the lesions they produce should be most intense in this region, and be continuous rather than segmental. Microscopically this is what actually does occur. On the other hand, it is rather difficult to imagine that a toxic substance in solution should suddenly loose its toxicity once it has passed a given point of the tubule. Oliver et al. state that more distal portions of the tubule do show tubulorhexis or disintegration of the tubular membrane, although in the crush syndrome the nephrotoxic lesion in the upper nephron is completely lacking.

In tubulorhexis when there is disintegration of the continuity of the tubular membrane, it is not surprising that there should be an interstitial tissue reaction. This is exactly what one would expect, and is precisely the same as what happens when the interstitial tissue is invaded by any other process such as occurs in pyelonephritis. In the latter, the response is inflammatory in nature.

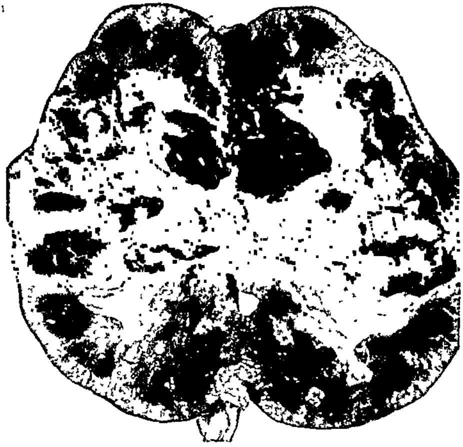


FIG. 4. Case No. 48-13883. Gross appearance of kidney in patient who died after partial recovery from acute renal failure Anuria developed following a 12 hour period of hypotension postoperatively Urinary output returned on the sixth postoperative day. Death occurred following evisceration of wound on sixteenth postoperative day.

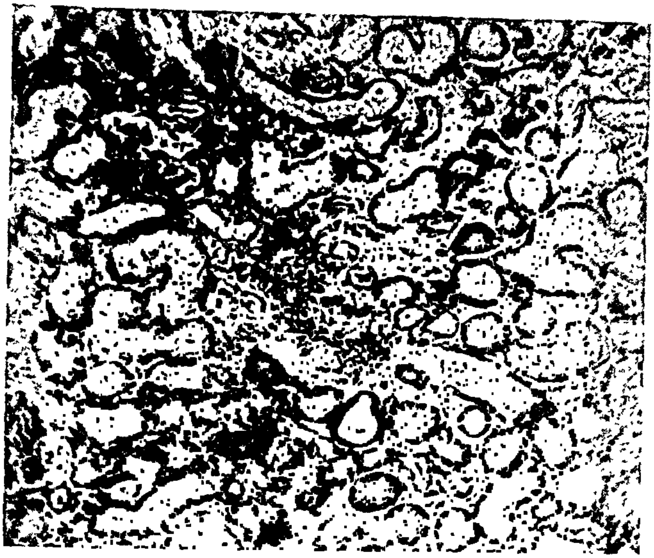


FIG. 5. Same case as figure 4. Microscopic section showing marked interstitial edema. Is it this edema which is choking off blood supply?

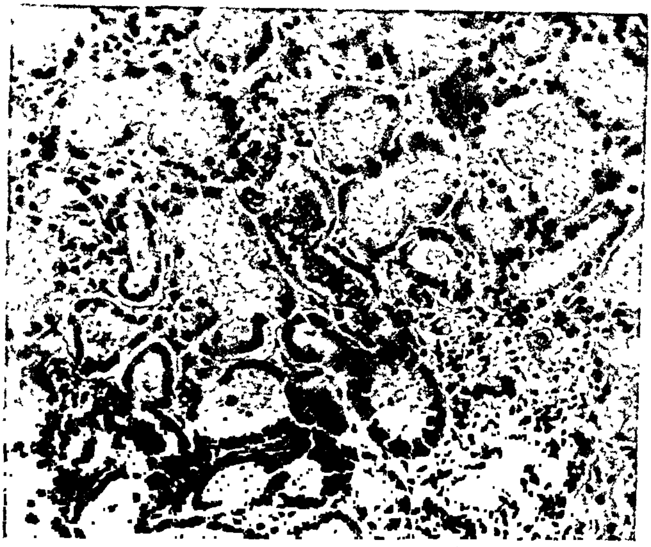


FIG. 6. Same case as figures 4 and 5. Microscopic section of another area showing haem pigment cast in tubule.

Figures 4, 5, 6, 7, and 8, from the author's cases, show some of the lesions described.

RENAL LESIONS IN EXPERIMENTAL CHOLINE DEFICIENCY

Hartroft has produced the "haemorrhagic renal syndrome" in experimental choline deficiency in weanlings and adult rats, and has described the pathogenesis. The initial lesion consists of the intracellular formation of sudanophilic droplets in the proximal convoluted tubules. He believes that the rapid appearance of the droplets may be responsible for the associated tubular swelling. This in turn causes pressure on the capillaries supplying the tubules, with resultant ischaemia and eventual necrosis of the tubules.

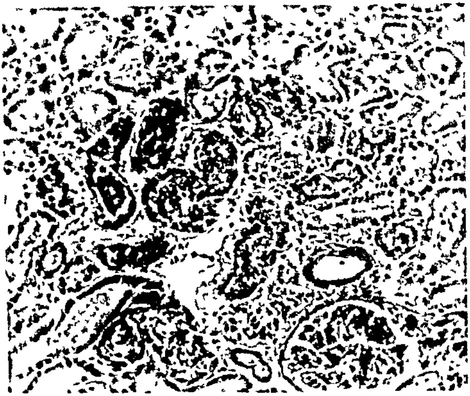


FIG 7. A-14194, case of retroplacental haemorrhage with death in uremia. Section shows casts in tubules with marked edema and infiltration around tubule. Tubule in lower left hand corner is disrupted (tubulorhexis).

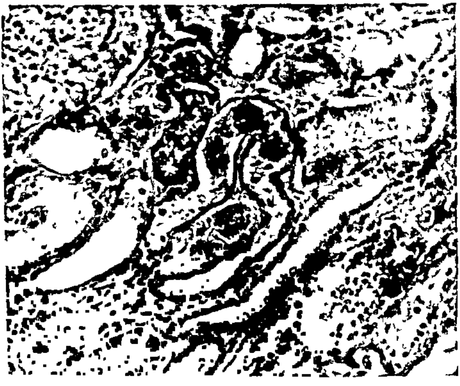


FIG 8. A-14281, case of post-transfusion anuria Section shows haem cast in tubule. Note that it is focal lesion, and that tubule both before it and after it is normal.

There would appear to be an extraordinary similarity between this type of lesion, and the nephrotoxic lesion described by Oliver et al.

In seeking a common denominator to explain the changes found in lower nephron nephrosis we must consider still other possibilities which might contribute to the production of this lesion. Referring back to figure 1, these are: the effects of:

1) Effective renal blood flow
2) Vasoconstriction of the efferent glomerular arterioles
3) Increased viscosity of the blood plasma, and stagnation

4) The effect of shock and anoxia on the liver and kidney
    a) Shock—Kidney produces V.E.M.—Vasoconstrictor
    b) Anoxia—Liver produces V.D.M.—Vasodilator
    c) Anoxia of kidney produces lower nephron nephrosis
5) Total sympathetic block
6) Trueta arteriovenous shunt
7) Barrie—Renal sponge
8) Collateral circulation

1) *Effective renal blood flow.* In man, 95 to 97 per cent of hippuran or diodrast added to human blood can be recovered from the plasma within 3 minutes. If for example 700 mg. of diodrast is excreted by the kidney in 1 minute, and the blood plasma has a content of 1 mg., it follows that 700 cc of plasma must have passed through the kidney in that period. This in turn represents a blood flow of 1300 cc per minute which is the normal effective renal blood flow in man for both kidneys.

It is possible to cannulate the renal vein and thereby measure the absolute renal blood flow. In some instances although the actual or absolute renal blood flow may remain unchanged, the effective renal blood flow may be considerably reduced as determined by para amino hippuric clearance tests.

Maluf, using India ink injections, has demonstrated in dogs that during the anuria or oliguria which follows the infusion of lysed red cells superimposed on reversible shock or dehydration, the cortex and medulla are equally injected with the dye, indicating a normal absolute blood flow, but there is a marked fall in the effective renal blood flow (as measured by renal clearance of parà-amino hippurate), due to the inability of the obstructed tubule to allow the passage of hippurate.

This was also well shown in one of the cases described in detail by Oliver et al. The patient was admitted to the hospital following the ingestion of anti-freeze mixture. The amount taken was unknown. He was admitted complaining of bilateral renal pain and dyspnea. Red blood cells and albumin were found in the urine. On the twelfth day the urine excretion was 0.2 cc per minute. The blood urea nitrogen was 266 mg. per cent and the para-amino hippurate and inulin extractions were zero.

The effective renal blood flow is lowered a) when the blood pressure is lowered, as in shock; b) when the blood volume is lowered as in haemorrhage, or marked dehydration; c) in crush and the lower nephron nephrosis type of lesion.

2) *Vasoconstriction of the efferent glomerular arteriole.* Some workers believe that the lesion in lower nephron nephrosis is initiated by a vasoconstricton of the efferent arteriole leaving the glomerulus. This in turn causes a stagnation of blood leaving the glomerulus, and is progressive in a retrograde manner to the glomerular tuft. Since the blood supply to the tubular portions of the individual nephrons is derived almost exclusively from the vascular network formed from the efferent glomerular arteriole, it follows that if vasoconstriction occurs, there results an ischaemia, which in turn produces anoxia of the tubules, leading to their degeneration.

3) *Increased blood viscosity leading to stagnation.* It is recognized that in uremia there is an increased vicosity of the blood plasma. This in turn may increase any stagnation already present in the renal circulation.

4) *The effect of shock and anoxia on the liver and kidney.* Shock is a clinical syndrome which is the result of a malproportion between the circulating blood volume and the volume of the vascular capacity, leading to metabolic changes which may be reversible or irreversible. If the blood pressure and blood volume fall, anoxia of the tissue occurs.

In reversible shock, the organism attempts to compensate for this constriction of the blood vessels of the skin, spleen, etc. to make blood available for the heart. During the anoxic period, the kidney produces a vasotropic substance V.E.M. which causes constriction of the arterioles. This in turn tends to maintain the blood pressure by diverting the blood from the periphery, and making it available to the essential organs, thus leading to recovery from the shock.

Anoxemia of liver: If, however, the stage of shock is continued beyond a certain period, the process becomes irreversible. The continued anoxemia exerts its effect upon the liver resulting in an altered metabolism, and the production of a vasodilator substance V.D.M. This substance has the opposite effect to V.E.M., and causes dilatation of all the arterioles of the body, resulting in pooling of the blood in the capillaries and arterioles.

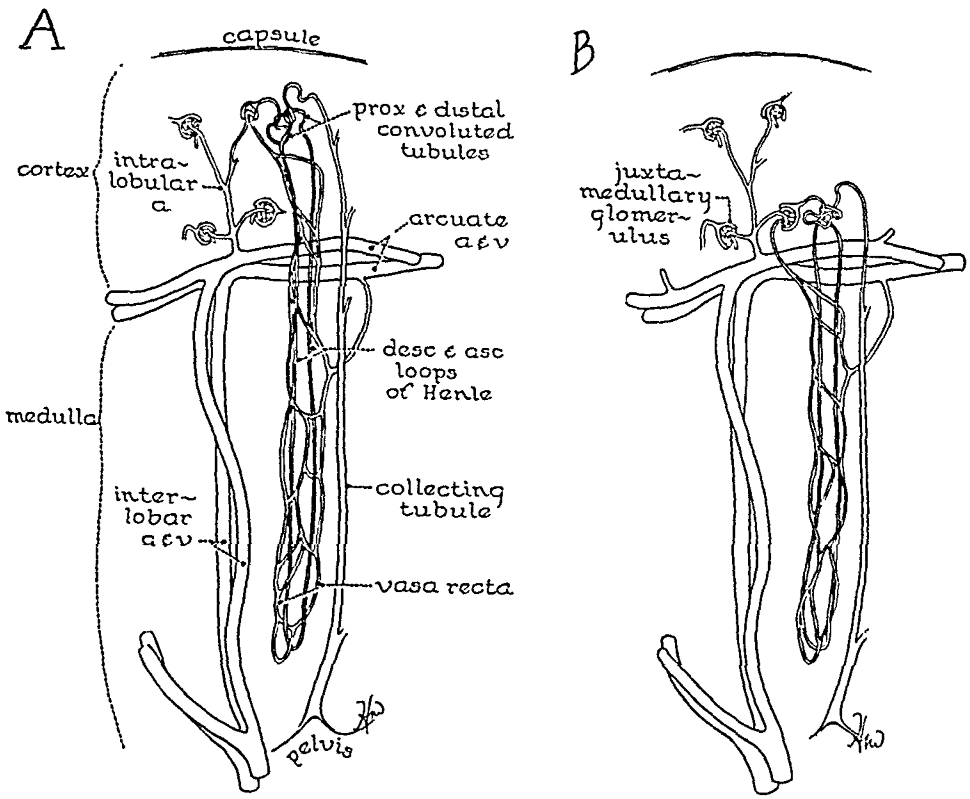
Anoxia of kidney: Glomerular filtration depends on the blood flow through the kidney, and blood pressure. In shock there is decrease in the blood flow through the kidney at a diminiished rate, and consequently there is a diminished volume of filtrate produced. This small amount of urine is reabsorbed by the tubules so that oliguria occurs, giving a urine with a high specific gravity. The tubules are as yet unaffected. The nonprotein nitrogen rises, but this is due to failure of filtration i.e., extrarenal uremia.

However, if the anoxia is maintained the tubules themselves become damaged and a true lower nephron nephrosis develops. The normal structure is lost and the normal functions of water absorption and selective reabsorption of waste products are also lost. The urine may now flow directly from the tubule into the blood. Haemoglobin casts will be found in the tubules. As the lower nephron nephrosis develops, it becomes a true renal uremia.

When liver damage due to anoxia occurs with renal failure, the condition is called "the hepato-renal syndrome."

5) *Total sympathetic block.* Griffiths and Gillies of Edinburgh working on "Total Sympathetic Block" have produced impressive observations, some of which are entirely contrary to what we have always believed.

In the cases reported, they intentionally produced a total sympathetic block so the surgeon could perform a thoraco-lumbar splanchnicectomy and sympathectomy. Premedication consisted of omnopon and hyoscine. In the anesthetic room, thiopentone was given intravenously, usually 1 gram. A lumbar puncture is done in the second lumbar space, and 150 to 250 mg. of procaine dissolved in 3 to 4 cc of cerebrospinal fluid injected. The patient is turned on his back and placed in sharp Trendelenberg position. This position is maintained until the



Normal

Trueta Shunt

FIG. 9. Indicating normal renal circulation, and diversion through "Trueta-shunt"

blood pressure starts to fall. An airway is inserted, and 100 per cent oxygen administered. The patient is then postured in the lateral "jack-knife" position. The blood pressure drops off to zero and stays unrecordable throughout the operation. The brachial and radial pulses are not palpable. The anesthesia is believed to extend up to and involve the first thoracic area, although this cannot be accurately determined as the patient is given thiopentone intravenously prior to the lumbar puncture.

In most cases an almost ischemic operative field is obtained. They report 84 operations involving 44 patients with only one death. (This patient had a pleural effusion on the opposite side.)

The interesting feature is that they regard the hypotension as perfectly harmless. Clinically, it has always been accepted that a minimal systolic pressure required to maintain effective filtration pressure was 75 mm Hg. They state, "At pressures lower than this, secretion of urine is much diminished and may even cease, but while effective ventilation with oxygen is maintained as in the technique described, viability of the renal epithelium is not endangered; when the systolic pressure rises to the level necessary for filtration, secretion of urine starts". In this series 3 patients showed a reduction in the output of urine during the first 36 hours after operation."

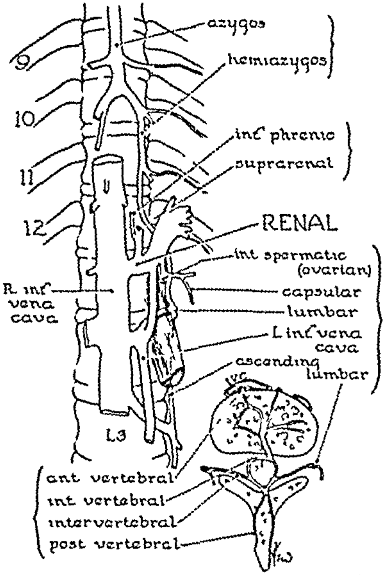


Fig 10 Showing collateral circulation of kidney Note that left renal vein is situated at center of a collection of venous channels 1) inferior phrenic and suprarenal tributaries from above, 2) communications with azygos and hemiazygos vein, 3) communications with set of internal and external vertebral plexuses via intervertebral and lumbar veins (Modified after Anson Surg, Gynec & Obst, 84 : 6, 1947)

The oxygen consumption of the normal and diseased human kidney has been studied by Cargill and Hickman, and by Clark and Barker

6) *Trueta arteriovenous shunt (juxtamedullary glomeruli)* Trueta and his associates have described two types of glomeruli designated cortical and juxtamedullary The juxtamedullary glomeruli are larger than the cortical The term cortical glomerulus is used to denote a glomerulus whose efferent vessel is of small caliber and which breaks up to form part of the cortical intertubular capillary network The term 'juxtamedullary glomerulus' is used to denote a glomerulus whose efferent vessel is of large caliber and which passes into the medulla to divide into vaso recti (fig 9) These workers believe that the kidney has two potential circulations, a greater and lesser Under extreme conditions, the blood may pass almost exclusively through one or the other Experimentally this may be true Clinically, there is no evidence in man that such a shunt does occur

7) *Barrie arteriovenous shunt* Barrie's work on the renal sponge would indicate that the renal medulla may have a blood supply independent of the glomerular circulation However, the conditions which Barrie described are found only in abnormal kidneys, and are probably not a normal structure Their relationship to acute renal failure has as yet not been clearly defined

8) *Collateral circulation* In certain cases of renal failure due to mechanical ob-

struction of the inferior vena cava, the collateral circulation of the kidney may be of paramount importance. The anatomy of the pararenal system of veins has been well described by Anson et al. (fig. 10).

On the right side the suprarenal vein and gonadal vein each empties separately into the inferior vena cava.

On the left side, the left renal vein is found to be situated at the center of a collection of venous channels: 1) the inferior phrenic and suprarenal tributaries from above; 2) communications with azygos and hemiazoygos vein; 3) communications with the set of internal and external vertebral plexuses via intervertebral and lumbar veins.

SUMMARY

In seeking a common denominator which would apply to the various factors discussed above, as contributing in the production of acute renal failure due to an intrinsic renal lesion, anoxia of the kidney or part of the kidney would appear to offer the most likely explanation.

The work of Selye on the General Adaptation Syndrome, and the possible effect of ACTH on the pathogenesis of acute renal failure have not been discussed. Although the theories behind this have considerable appeal, it is impossible to draw any conclusions at the present time.

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RENAL FUNCTION STUDIES IN POLYCYSTIC DISEASE OF THE KIDNEY: A PRELIMINARY REPORT

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Little information is available regarding discrete renal function studies in polycystic kidney disease. It is the purpose of this communication to report certain preliminary results obtained in the study of renal functions and electrolyte excretion in patients with this disease, evaluated prior to and following surgical decompression of the kidneys. The data include pre- and postoperative measurements of glomerular filtration rate (GFR), effective renal plasma flow (ERPF), maximum tubular secretion of p-aminohippurate (Tm_{PAH}), and renal excretion of sodium, chloride and potassium.

CASE MATERIAL

The present studies were performed on two adult male patients, both on active military duty at the time of diagnosis. The diagnosis of polycystic renal disease was based upon standard criteria, including dull persistent flank pain, bilateral palpable abdominal masses, and characteristic x-ray patterns following intravenous and retrograde urography. Case 1 (aged 40) was untreated prior to entrance into the hospital (fig. 1, *A*). Case 2 (aged 30) had been exposed to a surgical procedure for decompression of one kidney four months before the time of the present studies (fig. 1, *B*). Control data on case 1, therefore, precede surgical decompression of either kidney, whereas control data on case 2 precede decompression of the unoperated kidney. Postoperative studies were performed 5 weeks following surgery in case 1 and 6 weeks following surgery in case 2.

Surgical exposure of the kidney was performed through the usual lumbar approach. The operated kidneys were fully exposed and decompression was effected as completely as possible by excision of the larger cysts, destruction of the smaller cysts by multiple linear incisions through the cortex and aspiration of the deep cysts. An attempt was made to preserve normal parenchyma. Photographs of the kidneys before and after decompression are reproduced in figures 2 and 3.

METHODS

The pre- and postoperative studies were performed in the morning with the patients in the fasting state. One liter of water was administered 60–90 minutes before studies were begun. Additional water in 200 cc amounts was offered twice during the course of each series of clearance measurements in order to maintain urine flows in excess of 2 cc per minute.

Venous blood samples were drawn through an inlying 17-gauge thin-walled needle into heparinized syringes and discharged into heparinized tubes. A total of 0.1 cc of heparin was used per 10 cc of blood. Following each sampling of blood, 0.3 cc of a dilute (1:10) solution of heparin was instilled into the needle and the needle closed with a Luer-plug. Because no difficulty with clotting was experi-

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 6–8, 1953.

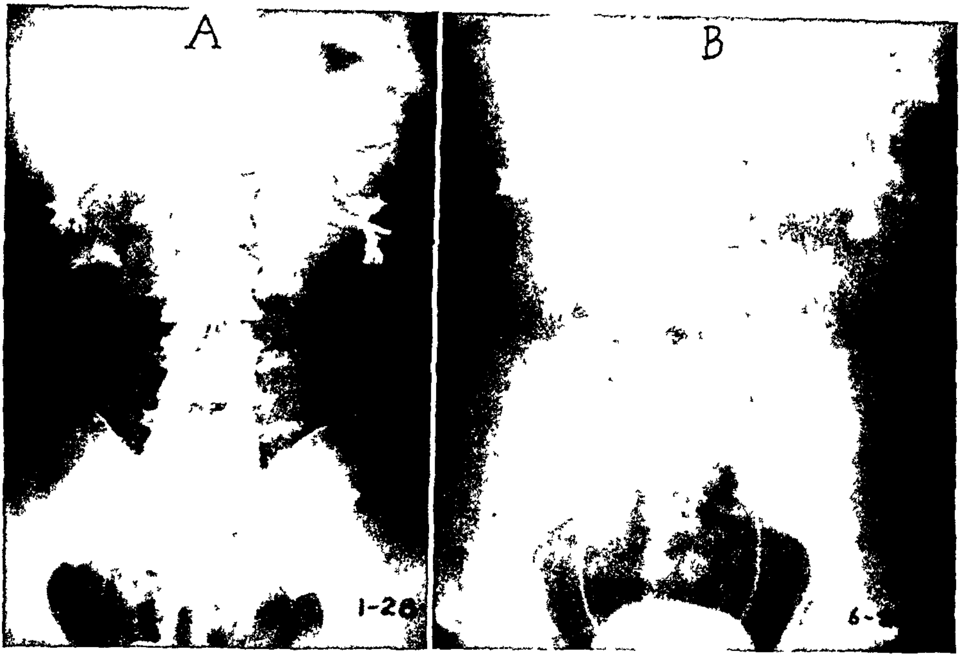

FIG. 1. *A*, retrograde pyelograms in case 1 prior to surgery. *B*, retrograde pyelograms in case 2 prior to surgery.

enced in runs up to five hours in duration, this method was preferred to the use of polyethylene catheters which frequently necessitated venous exposures. To prevent dilution from the heparin in the needle, a 2 cc blood sample was aspirated (in a separate syringe), and discarded prior to each sampling.

The bladder was catheterized with a multi-eyed rubber catheter. Two minutes before the completion of each urine collection period, bladder-washing was initiated. Two successive 10 cc aliquots of sterile distilled water were used, followed by two or more instillations of air. The latter was accompanied by suprapubic pressure. The total washout period was designed to last 2 minutes.

A timed urine sample and a blood sample were collected prior to administration of inulin and PAH primes for determination of inulin and PAH blanks. Prime injections were calculated to yield a plasma inulin concentration of approximately 30 mg. per cent and a PAH concentration of 2–3 mg. per cent.*

Sustaining infusions were administered in a normal saline vehicle through rubber tubing into the "inflow arm" using a constant infusion pump.† Sustaining solution A (inulin-clearance: C_{in}; and PAH clearance: C_{PAH}) was delivered at 1.5 cc per minute. Sustaining solution B (C_{in} and Tm_{PAH}) was delivered at 3.0 cc per minute. Rates of flow were calibrated at 15–30 minute intervals and were found to vary less than one per cent from the predicted rate.

Following administration of the priming injections and the start of sustaining solution A, a period of 30–40 minutes was allowed for equilibration of plasma

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[*] Inulin was obtained as 10 per cent solution from William R. Warner; PAH as sodium para-amino-hippurate in 20 per cent solution from Sharpe and Dohme; Heparin as heparin sodium injection from Lederle Laboratories.

[†] Bowman Infusion Pump Model 2: Process Instruments Co., 60 Greenpoint Ave., Brooklyn, 22, N. Y.

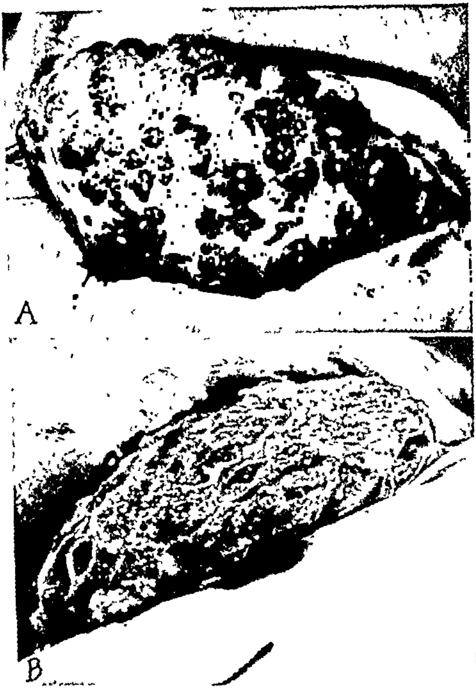

FIG. 2. Photographs of exposed kidney in case 1, before and after surgical decompression.

concentrations of inulin and PAH. Three to four 15–20 minute clearance periods were employed for determination of C_{in} and C_{PAH}. Priming for Tm_{PAH} measurements was accomplished by the administration of 60–70 cc of PAH through a three-way stopcock in the infusion tube at the rate of 10 cc per minute. A second period of equilibration was allowed and three 15–20 minute periods were employed for measurement in C_{in} and Tm_{PAH}. Blood was collected at the midpoint of each period and centrifuged immediately. Plasma was separated for analysis of inulin, PAH, Na, K, and Cl. Inulin was determined according to a modification of the method of Roe et al.[1] PAH was determined according to the method of Smith et al.[2] Chloride was determined according to the method of Van Slyke and Hiller.[3] Na and K were determined on a Baird internally compensated flame photometer.

[1] Roe, J. H., Epstein, J. H. and Goldstein, N. P.: A photometric method for the determination of inulin in plasma and urine. J. Biol. Chem., 178: 839, 1949.

[2] Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M.: The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Invest., 24: 388, 1945.

[3] Van Slyke, D. D. and Hiller, A.: Application of Sendroy's iodometric chloride titration to protein-containing fluids. J. Biol. Chem., 167: 107, 1947.

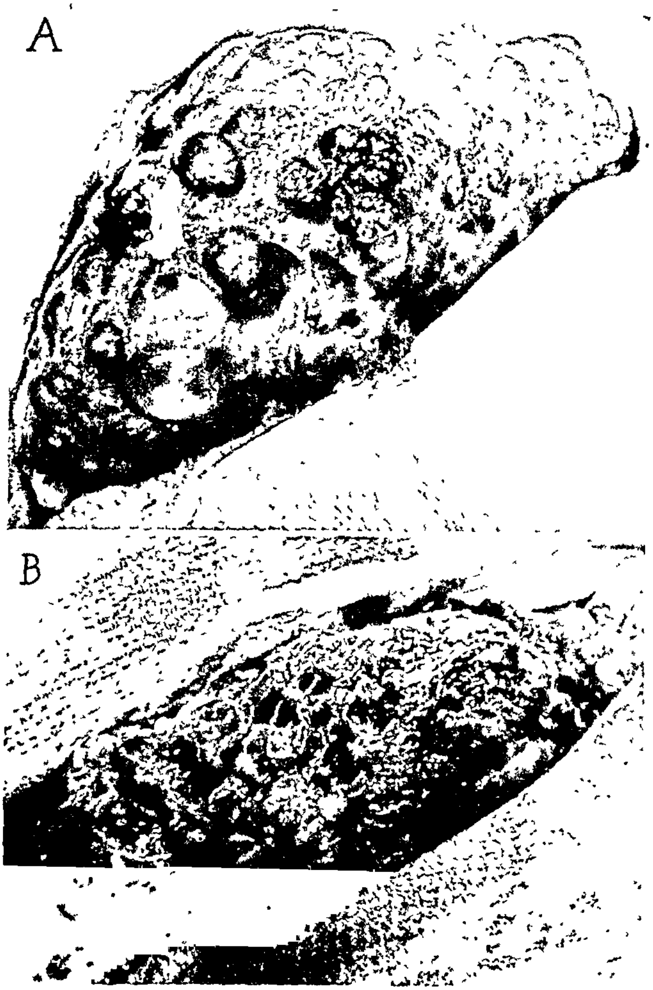

Fig. 3. Photographs of exposed kidney in case 2, before and after surgical decompression.

Plasma and urine inulin recoveries were run with each set of unknowns as a check on the degree of analytical accuracy. Recoveries averaged 100 per cent with extremes of 94 to 106 per cent. All inulin used was drawn from a single lot, which was found to be fructose free by yeasting aliquots prior to analysis by the resorcinol method.

Clearances were calculated by standard methods[4] without correction for delay time.

RESULTS

Average values for renal clearances are recorded in table 1.

Glomerular filtration rate. Low values for inulin clearance were obtained in both patients in control (i.e. preoperative) studies. The deviation from normal was more marked in the patient who had undergone previous decompression of one kidney (case 2), but, in this patient, the disease itself was more advanced.

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[4] Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease. New York: The Commonwealth Fund, 1944.

TABLE 1 *Renal function in polycystic disease of the kidneys Studies before and after surgical decompression of cysts*

	CASE 1			CASE II		
	Preoperative	Post operative	% Change post op	Preoperative	Post operative	% Change post op
C_{in} (prior to PAH loading)	85.5	79.7	−6.8	66.8	45.8	−31.4
C_{PAH}	383	366	−4.4	288	196	−29.2
F F × 100	22.5	21.8		23.2	23.4	
TM_{PAH}	77.4	60.3	−22.1	42.7	39.2	−8.2

Values represent the average of three or more successive determinations

Definition of symbols

C_{in} = inulin clearance (cc/min)

C_{PAH} = PAH clearance (cc/min)

F F = filtration fraction $\left(\frac{C_{in}}{C_{PAH}}\right)$

TM_{PAH} = maximal tubular excretion PAH (mg/min)

C_{in} values used in calculating F F were obtained prior to PAH loading

All values are corrected to 1 73 sq m body surface area

Following surgical decompression a further decrease in filtration rate was noted in both patients In case 1 the decrease in C_{in} was slight, in case 2 the decrease was more marked, amounting to 31 4 per cent of the preoperative value

Effective renal plasma flow Clearance of PAH tended to parallel C_{in} Both patients had control values considerably below normal Following surgery C_{PAH} declined slightly in case 1, and to a greater degree in case 2

Filtration fraction The ratio of $C_{in}:C_{PAH}$ was within the normal range[5] in both cases preoperatively Following surgery, filtration fractions remained essentially constant illustrating the parallel nature of the changes in C_{in} and C_{PAH}

Maximal tubular secretion of PAH The average preoperative value for Tm_{PAH} was normal in case 1 and depressed in case 2 Following surgery, Tm_{PAH} declined in both cases The greater decrease occurred in case 1, whereas C_{in} and C_{PAH} declined to a greater degree in case 2 In view of the known lability of Tm_{PAH} the magnitude of Tm changes cannot be interpreted at this time

Excretion of electrolytes Data on plasma concentrations and minute rates of excretion of Na, K, and Cl, together with computations of filtered load of Na and K are recorded in table 2 The figures for filtered load are uncorrected for plasma water content and the Donnan effect Computations of the per cent of filtered Na and K excreted ($C_{Na,K}$ C_{in}) are included to illustrate the change in electrolyte excretion following PAH loading in the postoperative as compared to the pre operative state The control values for this ratio are not intended to indicate the efficiency of tubular reabsorption of electrolytes

Sodium Plasma sodium values were within the normal range in all instances Following PAH loading, which imposes the necessity of excreting large amounts of anion, the excretion rate of Na increased abruptly in all experiments In both

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[5] Smith, H W The Kidney, Structure and Function in Health and Disease New York Oxford University Press, 1951

TABLE 2. *Renal excretion of electrolytes in polycystic disease of the kidneys before and after PAH loading (pre- and postoperative studies).*

PT.	STATUS	CONDITION OF EXPERIMENT	Cin cc/min.	Na				Cl		K			
				P_{Na} mEq/cc	F.L. mEq/min.	E.R. mEq/min.	$\frac{C_{Na}}{C_{in}} \times 100$	P_{Cl} mEq/cc	E.R. mEq/min.	P_K mEq/cc	F.L. mEq/min.	E.R. mEq/min.	$\frac{C_K}{C_{in}} \times 100$
1	*Pre-op.*	*Control (2)*	*80.9*	*.146*	*11.8*	.368	3.12	.111	.322	.0045	.366	.099	27.2
		PAH loading (2)	81.7	.147	12	.873	7.3	.109	.317	.0043	.352	.121	34.6
	Post-op.	Control (3)	79.7	.142	11.3	.249	2.3	.110	.209	.0038	.303	.075	24.63
		PAH loading (3)	67.8	.144	9.7	.60	6.2	.109	.161	.004	.271	.787	32.4
11	Pre-op.	Control (1)	84.2	.142	11.9	.498	4.2	.110	.426	.0045	.377	.094	24.9
		PAH loading (1)	97.4	.144	14.1	.767	5.5	.106	.331	.0038	.372	.079	21.2
	Post-op.	Control (4)	58.5	.144	8.35	.329	3.9	.109	.332	.0046	.269	.084	31
		PAH loading (3)	54.9	.147	8.08	.738	9.2	.108	.342	.0042	.232	.095	41.1

Number of determinations from which values are derived is indicated in parentheses.

Definition of symbols:

P_{NA}, P_{CL}, P_K = Plasma concentration of designated electrolyte;

F.L. = Filtered load (plasma concentration × C_{in}); E.R. = Excretion rate (urine *concentration × minute urine flow*); $C_{ELECTROLYTE}/C_{in} \times 100$ = *per cent filtered* load excreted; other definitions are included in Table 1.

Values for C_{in} are uncorrected for surface area.

cases, the ratio $\frac{C_{Na}:C_{in}(\text{Control})}{C_{Na}:C_{in}(\text{PAH load})}$ decreased following surgery. Although this is suggestive of a decreased ability of the tubules to retain Na postoperatively under the conditions of the experiment, alternate explanations are possible.

Potassium. Plasma K levels were consistently within the normal range. The ratio of $C_K:C_{in}$ was above that found in the presence of a normal filtration rate,[6] however the comments made above regarding this ratio appear to pertain to K as well as Na. The ratio $\frac{C_K:C_{in}(\text{control})}{C_K:C_{in}(PAH\ load)}$ decreased following surgery in both cases.

Chloride. Plasma chloride values were within the normal range in both cases in all studies. The effect of PAH loading upon the excretion rate of chloride was inconclusive.

DISCUSSION

There has been an increased interest in the surgical treatment of polycystic disease of the kidneys during the past decade as evidenced by the writings of Goldstein,[7] Cahill and Fish,[8] Dodson,[9] Rathbun,[10] Newman,[11] Howard[12] and others There is general agreement among these authors that in selected cases renal function is improved and life is prolonged by surgical intervention The mechanism by which this occurs is not clearly defined but the accepted explanation is that decompression of the kidney by rupture of the cysts results in release of untoward pressure on the remaining functioning nephrons

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[6] Earle, D. P., Farber, S. J., Alexander, J. D. and Pellegrino, E. D.: Renal function and electrolyte metabolism in acute glomerulonephritis. J. Clin. Invest., **30**: 421, 1951.

[7] Goldstein, A. E.: Polycystic renal disease with particular reference to author's surgical procedure. J. Urol., **66**: 163, 1951.

[8] Cahill, G. F. and Fish, G. W.: Surgical aspects of polycystic disease. Trans. Am. Assoc. G.-U. Surg., **34**: 81, 1941.

[9] Dodson, A. I.: Surgical treatment of polycystic disease of the kidney. J. Urol., **57**: 209, 1947.

[10] Rathbun, N. P.: Polycystic disease. Trans. Am. Assoc. G.-U. Surg., **35**: 131, 1942.

[11] Newman, H. R.: Congenital polycystic diseases. Am. J. Surg., **80**: 410, 1950.

[12] Howard, T. L.: Personal communication.

This present study cannot be considered as an assessment of the value of surgical treatment, since the follow up period is insufficient Temporary impairment of renal function is not infrequently observed following a variety of surgical procedures on the kidney, and when impairment already exists recovery from the surgical insult may be protracted Prolonged studies will be necessary to determine ultimate results

The possibility exists that the cystic nephrons may serve as functioning units In postmortem studies performed on two cases of polycystic disease, Lambert[13] was able to demonstrate inulin in the cyst fluid 15 and 96 hours after ante-mortem intraperitoneal inulin injection In studies performed in this laboratory[14] inulin has been administered intravenously to polycystic patients at the time of surgery and fluid has been aspirated directly from numerous cysts It has been found that inulin may appear in the cyst fluid within a matter of minutes in appreciable concentrations If the inulin entering the cysts can be attributed solely to glomerular filtration, the connection of the cysts to functional glomeruli appears likely * Further studies performed by Lambert[13] and by the present authors[14] have revealed a wide range of creatinine concentrations in fluid taken from different cysts in the same kidneys The presence of a gradient of creatinine concentrations suggests that the cysts may be intimately associated with functioning tubules, and the corollary exists that the more concentrated the creatinine the more distal the cyst lies along the course of the nephron Finally, postmortem reconstruction of cystic nephrons of polycystic kidneys by Lambert[13] and Norris and Herman[15] has revealed a glomerulo tubular continuity of cystic nephrons

This accumulation of data gives credence to the concept that the cysts are attached dynamically to functioning nephrons, and if this is true, the process of decompression of the kidneys by destruction of cysts may involve loss of multiple functioning units In light of this, it may be postulated that if the procedure is to improve function it must relieve compression of normal renal parenchyma sufficiently to compensate for this loss Further evaluation of these concepts is indicated

SUMMARY

Renal function and electrolyte excretion have been studied in 2 patients with polycystic renal disease before and after surgical decompression Function was depressed prior to surgery in both patients and further depression was noted 5 and 6 weeks following surgery

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* Studies are in progress to evaluate the possibility that some inulin may enter the cyst fluid by diffusion across the cyst wall

[13] Lambert, P P Polycystic disease of the kidney Arch Path , 44 34, 1947

[14] Bricker, N S , and Patton, J F Studies of the dynamics and chemical anatomy of cyst fluid in cystic disease of the kidneys (abstract) Clin Res Proc 2 22, 1954

[15] Norris, R F and Herman, L Pathogenesis of polycystic kidneys reconstruction of cystic elements in 4 cases J Urol , 46 147 1941

Plasma concentrations of Na, K, and Cl were within normal limits in all experiments. The excretion of Na and K relative to filtration rate was increased by PAH loading to a greater degree in the postoperative state than in the preoperative state.

The possibility that cystic nephrons contribute to renal function was discussed.

The authors give credit to Dr. C. A. Moyer who provided the stimulus for this study, and also acknowledge the invaluable assistance of Claude H. Schmidt, 1st Lt., M.S.C.; Ronald T. Caldwell, B.S., Pfc.; Doris C. Gomez, B.S.; and Melicent E. Hane, B.S.

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UPPER URINARY TRACT DISEASE ASSOCIATED WITH URETHRAL STRICTURE

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Stricture of the urethra in the male is a common disease and one that requires sustained treatment. In following the progress of numerous patients with urethral strictures it was observed by Beard and Goodyear[1] that co-existing disease of the upper urinary tract was seen with surprising frequency and usually as an incidental finding. Their observations stimulated our interest to investigate this subject further.

The association of upper tract disease with urethral stricture is mentioned in the textbooks, but the literature is scanty on the subject. A study of the literature reveals that Dourmashkin and Solomon[2] found the incidence of renal and ureteral calculi to be 22.6 per cent in their series of 84 men and women who had urethral obstruction. Birdsall[3] observed the frequency of hydronephrosis and renal calculi with obstructive lesions of the urethra.

With this in mind, a routine investigation of the upper urinary tracts of all patients with urethral strictures coming under observation over an 8 month period in the urological department of Grady Memorial Hospital in Atlanta was made. It is believed that the results of this study should be of interest.

This investigation was carried out on 152 consecutive patients with urethral stricture. Most of the strictures were sequellae of gonorrhea, the others were post-traumatic or postoperative. Twenty-seven patients were found to have additional obstruction to the lower urinary tract, these were excluded from this series. Those patients studied included 11 white and 114 Negroes. Ages of the patients ranged from 14 to 79, the majority being between 20 and 40 years of age. The strictures varied in severity from impassable to those well dilated.

In addition to pertinent history and examination of the urethra, routine investigation consisted of intravenous urography or retrograde pyelography or both, microscopic examination and culture of the urine, and blood chemistry studies of renal function.

Forty-seven of the 125 patients, or 37.6 per cent, were found to have one or more diseases of the upper urinary tract.

Twenty patients, or 16 per cent, were observed to have renal calculi. The calculi ranged from those barely recognizable to large, staghorn types. Eleven patients had a single stone, others had multiple stones. Bilateral calculi occurred in 3 patients. In conjunction, of those patients with stones, 8 had pyelonephritis, 5 had hydronephrosis, and 2 had hydro-ureter alone. Pyonephrosis occurred in 2 patients, both of whom had staghorn calculi.

Almost one fourth of the group demonstrated either hydronephrosis or hydroureter of varying degree.

Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26–29, 1953.

[1] Beard, D. E. and Goodyear, W. E.: Urethral stricture. A pathological study. J. Urol., 59: 619–625, 1948.

[2] [illegible] lomon, A. A.: Upper urinary tract lithiasis. A frequent [illegible] J. Urol., 48: 196–203, 1942.

[3] [illegible] lesions of the urinary tract and their relationship in the production of renal pathology. Clinics, 3: 70–89, 1944.

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ANTIBIOTIC THERAPY OF URINARY TUBERCULOSIS: AN INTERVAL REPORT OF SIX YEARS EXPERIENCE

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Over six years have now elapsed since the advent of antibiotic therapy in genito-urinary tuberculosis. In a preliminary report[1] 2 years ago, the cases of 64 patients treated at the University of Michigan Hospital for tuberculosis of the urogenital tract were reviewed. The present communication is a follow-up study of this original group together with data on 26 additional patients treated since that time. The most recent cases have been observed for a minimum period of 6 months after the completion of antibiotic therapy.

INCIDENCE

Of the 90 patients treated in this series, 57 were males and 33 females. The age of the patients varied from 18 months to 72 years with over two-thirds being between the ages of 20 and 50 years. The presenting signs and symptoms are summarized in table 1.

Fifty-three of the patients had concurrent active tuberculosis apart from the genito-urinary tract or gave a history of it. Forty-four of the 57 male patients had positive clinical evidence of genital involvement.

MODE OF TREATMENT

During the first 2½ years of study the patients received streptomycin in doses of 1.0 to 2.0 gm. daily for periods varying from 40 to 120 days. Since that time dihydrostreptomycin has been given, using a basic regimen of 2.0 gm. daily for 90 days. Seventy-five per cent of the patients in this latter group received a total of 180 gm. dihydrostreptomycin in 90 days. Because of circumstances arising during therapy, the remainder received variations from this basic program. Antibiotics have been used to augment rather than supplant the well established principles used in combating tuberculosis, and for this reason sanatorium care during antibiotic therapy and for 6 to 12 months following medication has been considered essential. All cases in this series were studied by cystoscopy, retrograde pyelography and renal function tests; and 24 hour bladder urine as well as individual kidney specimens were tested by culture methods and guinea pig inoculation.

Para-amino salicylic acid has been used in treating our patients since the value of this substance has been recognized, but we have continued to employ daily 2.0 gm. doses of the antibiotic even though most investigators today advocate a smaller dosage given less often. There are certainly valid reasons for the latter regimens but their ultimate value has yet to be assessed. Many phthisiologists have urged us to continue with the regimen of large daily dosage so as to provide a basis for comparison of long term results with other plans of treatment, and

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6-8, 1953.

[1] Nesbit, R. M., and Thirlby, R. L.: Results of streptomycin therapy in urinary tuberculosis; A four year review. J. Urol., 68: 394-398, 1952.

TABLE 1. *Presenting symptom or sign*

	CASES
Irritative bladder symptoms	40 patients
Epididymitis	17 patients
Hematuria	13 patients
Pyuria	13 patients
Flank pain	7 patients

since this series comprises a significant number of cases the policy would appear to be justified until some regimen had demonstrated a clearly defined superiority.

The present program then consists of complete rest in a sanatorium, dihydrostreptomycin 2 gm. daily, and PAS 12 to 15 gm. daily. Isoniazid is used as an addition to this regimen when a second course of therapy is used either for relapse cases or those which fail to respond to the initial 90 day course.

In unilateral renal disease, when small lesions are demonstrated in the pyelogram, antibiotic therapy is administered for 60 days then a check-up examination is made If substantial improvement has not occurred, nephrectomy is performed and the antibiotic program is continued for another 30 days. If initial pyelograms demonstrate a moderate or advanced destructive process, then nephrectomy is performed after 10 days of antibiotic therapy and the regimen is continued through 90 days. All patients have check-up studies with x-rays at the completion of the antibiotic regimen and at 3 month intervals for the first year; every 6 months thereafter. Urine cultures and animal inoculation studies are carried out monthly for the first year.

RESULTS OF TREATMENT

Unilateral renal disease was treated in 42 patients (table 2). Sixty-seven per cent of this group had normal urine when last examined. Twenty-one of the unilateral cases were treated with nephrectomy as well as antibiotics and 86 per cent of these have remained well. An equal number of unilateral cases did not have surgery and lasting remission occurred in only 48 per cent. The results of medical treatment alone certainly do not compare favorably with the combined surgical and antibiotic regimen in this small group of cases; and the high failure

TABLE 2. *Unilateral renal disease*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
No surgery			
Normal pyelograms	13	7	53 8
Minimal abnormality	4	2	50
Moderate abnormality	4	1	25
Total no surgery	21	10	47.6
Nephrectomy—all had abnormal pyelograms	21	18	85 7
Total all cases	42	28	66 7

rate in the cases showing normal pyelograms offer a strange paradox when compared to the high rate of remission that has been observed in the bilateral cases of the present series.

Table 3 summarizes the results of treatment in patients with bilateral renal tuberculosis. There were 30 patients in this group and 76 per cent have enjoyed remissions to date. The majority of these bilateral cases had one kidney removed either prior to the present program of antibiotic therapy or else in conjunction with the regimen. Table 4 enumerates the status of the kidneys in the bilateral cases in which surgery was not performed. It is of interest to note that 4 of 6 patients with significant bilateral pyelographic changes developed normal urine and have not relapsed. X-rays in 2 of these cases are of considerable interest so are included in this report (figs. 1 and 2).

Eighteen patients had negative kidneys but had tuberculous cystitis and/or genital involvement. Ten of these had a previous nephrectomy with the remain-

TABLE 3. *Bilateral renal disease*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Previous nephrectomy, normal x-ray	8	7	87.5
Previous nephrectomy, abnormal x-ray	5	4	80
Nephrectomy with treatment normal x-ray remaining kidney	4	3	75
Nephrectomy with treatment, abnormal x-ray remaining kidney	1	1	100
No surgery	12	8	66.7
Total	30	23	76 6

TABLE 4 *Bilateral renal disease without nephrectomy; results classified according to pyelographic findings*

PYELOGRAMS	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Normal to minimal abnormality on both sides	2	1	50
Normal to minimal abnormality on one side Moderate to advanced abnormality opposite side	4	3	75
Moderate to advanced abnormality on both sides	6	4	66.7
Total	12	8	66.7

TABLE 5. *Residual cystitis and/or genital tuberculosis*

	NUMBER OF PATIENTS	CONVERSION OF URINE TO NEGATIVE	% CONVERSION OF URINE TO NEGATIVE
Previous nephrectomy, normal x-ray	10	8	80
Normal x-rays, kidney urines negative	8	6	75
Total	18	14	77.7

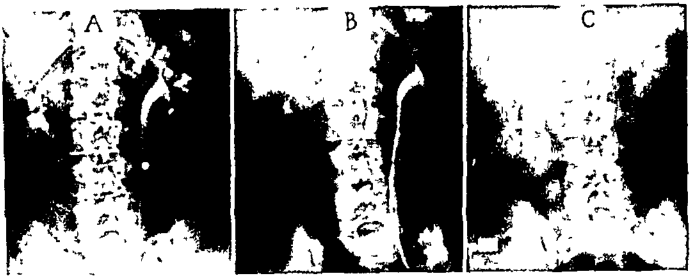

FIG. 1. V. T., a woman aged 29 with bilateral renal tuberculosis. History of pulmonary tuberculosis 1941; Potts's disease 1945. *A*, pyelogram, June 1948, prior to treatment. Patient was given streptomycin 2 gm. daily for 113 days (June–October 1948). Urine became negative after treatment and has remained negative until present time. *B*, 13 months after treatment. *C*, 4½ years after treatment. Note evidence of function on left side revealed by filling of micropelvis with excreted contrast medium. Patient has remained clinically well, and urine has been free from tuberculosis 4½ years.

ing kidney clinically free of disease. The remaining 8 patients had normal pyelograms as well as negative culture and guinea pig studies from both kidneys, yet had tubercle bacilli in the voided urine. Fourteen of these patients had a favorable response to therapy (78 per cent). The results are summarized in table 5.

SUMMARY OF RESULTS

Sixty-five of the 90 patients have had a conversion of urine to negative and have remained clinically free from urogenital tuberculosis 6 months to 6 years after treatment (table 6). Fifty-five had favorable response after one course of therapy, while thirty-five were initial failures or else relapsed after a temporary remission. Twenty-four of these 35 failures were given a second course of treatment and 9 became free from tubercle bacilli after treatment. Two patients received a third course of treatment and one of these exhibited negative urine after treatment (20 months at the present time), while the other relapsed 10 months after the third course of the antibiotic.

Streptomycin was used in 46 of the 116 courses of treatment and yielded a remission rate of 52.2 per cent, while 58.8 per cent of 70 dihydrostreptomycin courses resulted favorably. There is no significant difference in the 2 groups (table 7).

TOXICITY

Toxic manifestations in the 116 courses of therapy are summarized in table 8. In this series the incidence of reactions was materially greater with streptomycin although this antibiotic had the advantage of producing no apparent damage to the auditory branch of the VIII cranial nerve.

ANALYSIS OF FAILURES

In 25 cases the patients failed to respond favorably to therapy. This group represented 51 failures when measured in terms of total courses of treatment with or without nephrectomy. Table 9 shows the distribution of relapses by the month

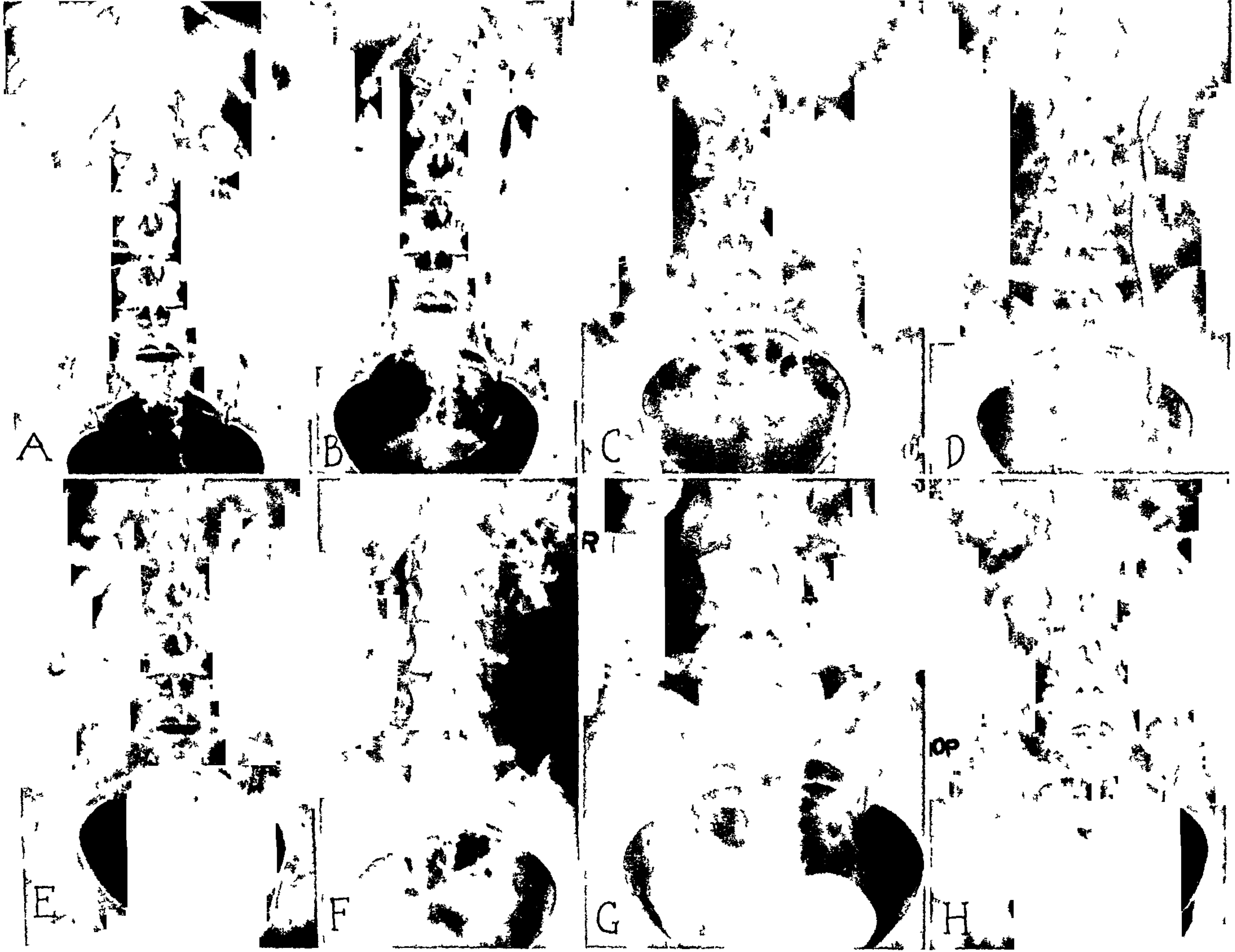
A
B
C
D
R
E
F
G
OP
H

FIG 2 L D , a woman aged 22 with bilateral renal tuberculosis proven by culture and guinea pig inoculation of urine from each kidney History of pulmonary tuberculosis 1943, *tuberculous peritonitis* 1946 *A*, excretory urogram prior to admission to University Hospital *B*, retrograde pyelogram (University Hospital) June 1946 Bilateral disease Note constriction of left renal pelvis Patient received streptomycin 1 5 *gm* daily for 70 days beginning June 1947 Urine normal at end of treatment *C*, excretory urogram, September 1947, at end of treatment Note bilateral hydronephrosis *D* retrograde pyelogram, September 1947 showing nearly *complete stenosis* of left pelvis Right cutaneous ureterostomy, September 1947, because of impassable stricture of right ureteral orifice *E*, retrograde pyelogram showing improvement of right hydronephrosis 1 month *following cutaneous ureterostomy* Note also marked improvement on left that has occurred in 1 month After 18 months on cutaneous ureterostomy, patient demanded that something be done to rid her of that unhandy device In April 1949 *right ureter was re implanted* into bladder by attaching short upper ureter to tube fashioned from dome of bladder *F*, excretory urogram made 1 month following re implantation of ureter *G*, cystogram made 1 month *following re implantation of* ureter Note reflux *H*, excretory urogram, October 1952, shows no hydronephrosis in either kidney On left, upper calyx does not visualize but constrictive process that was present in pelvis in 1946 and 1947 has *cleared completely* Patient now clinically well, and urine has remained free from tuberculosis 6 years Patient married 2 years ago

TABLE 6. *Response of urinary tuberculosis to streptomycin and/or dihydrostreptomycin with or without nephrectomy (90 cases)*

	TOTAL	CONVERSION OF URINE TO NEGATIVE
First course	90	55
Second course	24	9
Third course	2	1
Total		65 = 72%

TABLE 7. *Results obtained in 116 courses of streptomycin or dihydrostreptomycin therapy*

	COURSES OF THERAPY	CONVERSION URINE TO NEGATIVE	FAILURE OR RELAPSE	% CONVERSION URINE TO NEGATIVE
Streptomycin	46	24	22	52.2
Dihydrostreptomycin	70	41	29	58.5
Total of all courses	116	65	51	56

TABLE 8. *Reactions to streptomycin and dihydrostreptomycin in 116 courses of therapy*

	COURSES OF THERAPY	VESTIBULAR	AUDITORY	ALLERGIC	% REACTION
Streptomycin					
Less 100 gm .	9	0	0	2*	22.2
100–200 gm.	27	13	0	1*	51.8
220–300 gm. .	10	3	0	0	30
Total	46	16	0	3	41.3
Dihydrostreptomycin					
Less 100 gm.	14	4	1	1*	37.5
100–200 gm.	53	8	5	1*	26.4
200–300 gm.	3	0	0	0	0.00
Total	70	12	6	2	28.6
Total all courses	116	28	6	5	34.5

* Drug discontinued.

following completion of therapy. It would appear to be significant that the great majority of relapses occurred within the first 6 months, and that no relapses have occurred thus far after 10 months. In this connection it is of interest to note that in the group that Nesbit and Thirlby reported before this society 2 years ago, all of the patients who were then reported to be clinically free from urogenital tuberculosis have remained negative.

For purposes of analysis the 25 patients that failed to respond to treatment or relapsed can be divided into 3 groups:

1) Eleven patients had unilateral renal tuberculosis with normal or abnormal pyelograms on the affected side and were not operated upon. (Three since have had nephrectomy—within the past 6 months).

TABLE 9 *Time distribution of 51 relapses or failures*

• — First course
\ — Second course
* — Third course

Number of relapses	0	1	2	3	4	5	6	7	8	9	10	11	12
10													
9	\												
8	\		\		\								
7	•		\		•								
6	•	\	\	\	•		\						
5	•	\	•	\	•		\						
4	•	•	•	•	•		\						
3	•	•	•	•	•		•	\	•				
2	•	•	•	•	•		•	\	•				
1	•	•	•	•	•		•	•	•		•		

Months following therapy

2) Seven with normal kidneys or who had nephrectomy and antibiotics for treatment of unilateral disease remained positive due to persisting cystitis and/or genital tuberculosis

3) Seven patients with bilateral disease

SUMMARY

In a series of 90 patients with urogenital tuberculosis, 72 per cent (65 cases) have exhibited negative urine for 6 months to 6 years following the completion of therapy

A therapeutic program of 2.0 gm a day of streptomycin or dihydrostreptomycin for 90 days with sanatorium care 6 to 12 months has been used and still is advocated, along with the uses of PAS and isoniazid It is our purpose to continue with this plan of therapy in the hope that a comparison with reports of other series of patients who are treated with other programs may eventually reveal just what plan of treatment is the best in yielding long term results

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A TECHNIQUE FOR INTERMITTENT OR CONTINUOUS IRRIGATION OF THE RENAL PELVIS

JAMES H. SEMANS* AND HENRY F. LAGUETTE

Certain factors are desirable in any technique for intermittent or continuous irrigation of the renal pelvis, especially when solutions of low pH are used. The fever produced should be minimal. The procedure should not affect permanently the caliber of the ureter or the function of the kidney. The pain should not be sufficient to require deep narcosis. The unanesthetized, hospitalized patient should be able to perform the irrigation with safety, and without constant supervision, over a period of several days.

Since 1945, one of us (J. H. S.) has been using a method which is reported here because it has met these requirements. Six patients performed the irrigation on 11 occasions. The febrile reaction was mild. There was no evidence of late or permanent renal damage demonstrable by microscopic examination of a kidney removed 2 years after irrigation (case 6). The excretion of phenolsulfonphthalein increased; and the nonprotein nitrogen in the blood was not elevated. After the patient learned the amount of irrigating fluid tolerated the pain was usually controlled by codeine in dosage of ½ or 1 grain. Demerol and morphine were used as indicated. There was no constant supervision necessary. As much as 500 cc of solution M[1] passed through the renal pelvis in 24 hours. Pyelograms made after irrigation demonstrated no ureteral stricture, with the exception of one case in which hydro-ureter was present before irrigation.

The indications for irrigation were small residual calculi impacted in a calyx (cases 1, 2, 3, 4 and 5), incrusted pyelitis diagnosed at the time of removal of large phosphatic calculi (cases 3, 4 and 5) and chronic symptomatic pyelonephritis, refractive to prolonged and repeated antibiotic therapy (case 6). Irrigation was always used as an adjunct to the usual therapeutic measures. Citric acid adjusted to pH 4.5 was alternated with normal saline. The gross character of the urine changed from cloudy to clear approximately a week following completion of the procedure. This improvement was always temporary and could have been attributed to the antibiotics.

PREPARATION OF THE PATIENT

One week before irrigation, the patient is studied by means of urine culture, tube sensitivity test, determination of the nonprotein nitrogen of the blood and by excretion of phenolsulphonphthalein for a period of 2 hours, at half-hour intervals.

The tube sensitivity test is used to select the antibiotic always given to prevent fever and bacterial contamination of the blood stream during irrigation. If this test is not available, a combination of penicillin and streptomycin is injected before pyelography and continued once or twice each day, until the patient can

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Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26-29, 1953.
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take medication orally Chloromycetin can then be given by mouth in dosage of 500 mg every 8 hours These drugs prevent the blood culture from becoming positive and minimize the mucus and pyelonephritis associated with the procedure Their administration is begun one day before the irrigation and is continued afterward until the patient remains afebrile without them for at least 48 hours

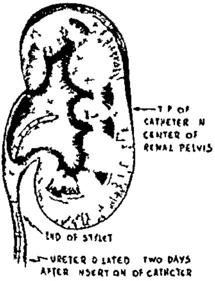
Determination of the nonprotein nitrogen and excretion of phenolsulphonphthalein before the irrigation is useful for comparison with values obtained afterward

TECHNIQUE

A No 5 graduated opaque catheter with whistle tip is passed to the renal pelvis A stylet of wire remains in place, with the tip withdrawn 10 cm from the end lying in the kidney The wire is forcibly bent at a sharp angle over the end of the catheter and cut off a few millimeters beyond the angled end See figures 1 and 2 After x-ray films have shown the tip of the catheter in the center of the renal pelvis, or any other desired area, the bladder is emptied and the cystoscope removed Care is taken to avoid moving the catheter during this maneuver

A No 20 Foley-Alcock catheter with 5 cc bag is next placed in the bladder and the balloon inflated Another x-ray film is exposed, since it is essential that the catheter in the ureter be left in the exact position required

The two catheters are then fastened together A silk ligature is tied tightly around the Foley-Alcock catheter and then around a narrow strip of adhesive,


TIP OF CATHETER IN CENTER OF RENAL PELVIS
END OF STYLET
URETER DILATED TWO DAYS AFTER INSERTION OF CATHETER

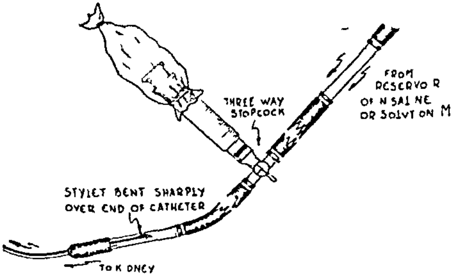

THREE WAY STOPCOCK
FROM RESERVOIR OF SALINE OR SOLVENT
M
STYLET BENT SHARPLY OVER END OF CATHETER
TO KIDNEY

FIG 1 FIG 2

FIG 1 Schematic drawing of renal pelvis containing No 5 graduated opaque catheter with whistle tip Stylet of wire is 10 cm from end of catheter, which lies in center of renal pelvis

FIG 2 Detailed drawing of inset marked in figure 3 by heavy black circle Small surgical drain of Latex is ligated on one end, stretched and ligated around 2 cc syringe having Luer lok After sterilization syringe is attached to 3 way stopcock, which is interposed by Latex and glass adapters into irrigation system, next to ureteral catheter leading to kidney Perforated small rubber tip, standard accessory of cystoscope, is used on ureteral catheter This apparatus enables patient to introduce either sterile saline, or solution on clinical trial as solvent through ureteral catheter into renal pelvis intermittently, as tolerated Later stopcock is set for continuous flow (see text under technique of irrigation)

3 mm. in width, which, in turn, is wrapped around the catheter coming from the ureter. Next, the long ends of the same silk ligature are tied over the adhesive now covering both catheters. The same procedure is repeated on both catheters a few centimeters distally. It is our experience that this method prevents any but the slightest change in the catheter's position in the kidney during the entire period of irrigation. The catheter in the urethra is then fixed to the penis with adhesive tape.

For the first 2 days, the patient is instructed to distend the pelvis with 2 cc of sterile normal saline solution intermittently (fig. 3). He soon learns to increase the amount, without producing renal pain. The fluid is injected by means of the aseptic closed apparatus illustrated in the drawing (fig. 2).

Five cubic centimeters of sterile indigo carmine solution is added to the reservoir of normal saline. After 2 or 3 days, the fluid coming from the catheter in the bladder becomes blue. This is an indication that the ureter has dilated sufficiently around the inlying catheter to accommodate a continuous flow. A rate of 60 drops per minute is tolerated.

Once this has occurred, the more irritating solution M is introduced. It is used alternately with the saline solution, frequently enough to prevent renal pain. A total of 500 cc of solution M can be tolerated in the pelvis during 24 hours. As soon as pain begins, solution M is stopped, and saline solution substituted. The discomfort should not exceed the therapeutic effect of 1 grain of codeine. Mucoid detritus may occlude the catheter in the urethra and necessitate removal by the usual technique of irrigation.

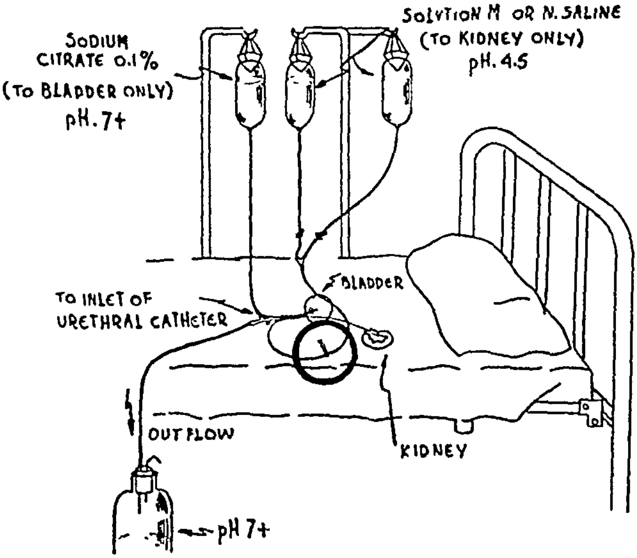


FIG. 3. On far right is reservoir for normal saline solution. Patient can regulate flow by screw clamp. A y-tube separates this solution from solution M or other solvent in next reservoir to left, so that patient can substitute either solution for the other, in case renal pain occurs with continued introduction of solvent. Reservoir on far left supplies alkaline solution (sodium citrate) to raise pH of vesical contents. Solution flows continuously through inlet tube into bladder at a rate controlled by patient with screw clamp. Patient introduces fluid into kidney intermittently, at first, by syringe illustrated in detail in figure 2.

Sodium citrate, 0.1 per cent, runs continuously into the inlet tube of the Foley Alcock catheter (fig. 3) at a rate of flow sufficient to raise the pH of the vesical urine to 7 (checked with nitrazine paper by the patient). This minimizes pain in the bladder.

CASE ABSTRACTS

Case 1. J. J. A., McGuire General Hospital, Richmond, Va., registration No. 1900, admitted February 28, aged 48 years. Diagnosis: Calculus, calyceal, left kidney, following pyelolithotomy. Duration of irrigation: 7 days. Comment: Pyelogram made 1 week and 3 months after irrigation showed no evidence of calculus.

Case 2. R. C. S., McGuire General Hospital, Richmond, Va., registration No. 5005, admitted 1945, aged 19. Diagnosis: Calculi, miliary, multiple (prolonged recumbency). Duration of irrigation: 5 days. Comment: No improvement. After ambulation, patient passed many calculi. Only one opaque shadow remained.

Case 3. H. A. F., Piedmont Hospital, Atlanta, Ga., registration No. 114818, admitted January 8 through January 18, 1950, aged 47 years. Diagnosis: 1) Solitary kidney; 2) incrusted pyelitis (observed at time of removal of large staghorn calculus). Duration of irrigation: 6 days. Amount used: 3000 cc solution M. Highest temperature recorded: 99F. Antibiotic given: Chloromycetin. Laboratory data: Nonprotein nitrogen, 34.1 mg. per cent, before irrigation, 30.0 mg. per cent, after irrigation; phenosulfonphthalein output, 64 per cent in 2 hours, 11 months after irrigation.

Second irrigation: Admitted August 9 through August 19, 1950. Diagnosis: Small recurrent calculi (two) in solitary kidney. Duration of irrigation: 5 days. Amount used: 3000 cc solution G. Highest temperature recorded: 99F. Antibiotic given: Penicillin, streptomycin and chloromycetin. Laboratory data: Nonprotein nitrogen, 23 mg. per cent, before irrigation; phenolsulfonphthalein output, 52 per cent in 2 hours, 8 months after irrigation.

Third irrigation: Admitted: March 11 through March 24, 1951. Duration of irrigation: 6 days. Amount used: 3000 cc solution G. Highest temperature recorded: 99F. Antibiotic given: Chloromycetin. Laboratory data: Nonprotein nitrogen; 34.8 mg. per cent, before irrigation, phenolsulfonphthalein, 56 per cent in 2 hours, before irrigation, 52 per cent after irrigation.

Fourth irrigation: Admitted: August 30 through September 11, 1952. Duration of irrigation: 5 days. Amount used: 3000 cc of solution G. Highest temperature recorded: 99F. Antibiotic given: Chloromycetin. Laboratory data: Nonprotein nitrogen, 25 mg. per cent; phenolsulfonphthalein, 66 per cent in 2 hours, before irrigation.

Case 4. J. M. M., St. Joseph's Infirmary, Atlanta, Ga., registration No. 5246, admitted November 30 through December 13, 1949, aged 27 years. Diagnosis: 1) Calculus, left kidney; 2) pyelonephritis, chronic. First irrigation: Duration, 6 days. Amount used: 3000 cc solution G. Highest temperature recorded: 100.2F. Antibiotic given: Chloromycetin. Laboratory data: Phenolsulfonphthalein output, 45 per cent in 2 hours, 6 months before irrigation; 59 per cent in 2 hours, 2 years after irrigation; 68 per cent in 2 hours, 3 years after irrigation.

Second irrigation: Admitted: August 14 through August 27, 1952. Duration of irrigation: 6 days. Amount used: 3000 cc solution G. Highest temperature recorded: 100F. Antibiotic given: Chloromycetin.

Case 5. M. L., Piedmont Hospital, Atlanta, Ga., registration No. 119788, admitted September 10 through September 22, 1950, aged 43 years. Diagnosis: Calculi, left kidney. Duration of irrigation: 5 days. Amount used: 1000 cc in 48 hours (solution G). Highest temperature recorded: 101F. Antibiotic given: Chloromycetin. Narcotics used: Codeine, ½ grain; Demerol, 100 mg.; morphine, ⅙ grain. Laboratory data: Nonprotein nitrogen, 23 mg. per cent, 1 month before irrigation, 34 mg. per cent, 2 years after irrigation; phenolsulfonphthalein, 47 per cent in 2 hours, before irrigation; 64 per cent in 2 hours, 2 years after irrigation.

Case 6. J. L. H., St. Joseph's Infirmary, Atlanta, Ga., registration No. 4918, admitted September 11, 1950, aged 46 years. First irrigation: Diagnosis: chronic pyelonephritis, symptomatic. Duration of irrigation: 10 days. Amount used: 3000 cc solution G. Highest temperature recorded: 100.4F. Antibiotic given: Chloromycetin. Narcotics given: Demerol, 100 mg. Laboratory data: Nonprotein nitrogen, 24.5 mg. per cent, last day of irrigation; phenolsulfonphthalein output, 29 per cent in 2 hours, 2 years after irrigation.

Second irrigation: Admitted: July 8 through August 2, 1952. Amount used: 1000 cc solution G. Duration of irrigation: 5 days. Highest temperature recorded: 101.2F and 102.8F. Antibiotic given: Penicillin, streptomycin and terramycin. Laboratory data: Nonprotein nitrogen, 30 mg. per cent, before irrigation; phenolsulfonphthalein output, 29 per cent in 2 hours, before irrigation, 47 per cent in 2 hours, 12 days after irrigation. Nephrectomy: 2 weeks after irrigation. Microscopic diagnosis: Low grade pyelonephritis (St. Joseph's Infirmary, Path. No. 12317). Comment: Indication for nephrectomy: Persistent nephritis, febrile, symptomatic, refractive to antibiotics for 2 years.

DISCUSSION

This technique for irrigation of the renal pelvis has proved valuable in the clinical trial of solvents for certain types of urinary calculi. Except for the disappearance of small calcified shadows in 2 cases, no dissolution was evident in the other patients.

In one of these, a calculus was passed soon after completion of irrigation. Approximately 1 week after irrigation, urine, which had been grossly cloudy and mucoid previously, became temporarily clear. Since antibiotics were used in all patients, this improvement could not be attributed to the procedure of irrigation.

Suby[1] has stated that a solvent is relatively impractical unless a calculus can be completely dissolved in 50 to 75 hours. This technique would comply with this requirement, since the irrigation continued over a period of 48 hours to 10 days. Clinical reports of the use of solutions now available, such as G, M and Versene, do not indicate that these agents can be successful in any significant number of cases. However, the value of solution G in the dissolution of vesical incrustation, can often be confirmed by cystoscopy For this reason, it was used when incrusted pyelitis was observed at the time of operation for removal of the calculus

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[1] Suby, H. I.: Dissolution of urinary calculi. J. Urol., **68**: 96, 1952.

The principle of using a dilated ureter to drain irrigating fluid from the renal pelvis, was illustrated by Kelly and Burnam (drawing by Max Brodel) in 1922 [2]

SUMMARY

A technique for irrigating the renal pelvis by intermittent or continuous flow, is described for clinical trial of solvents of urinary calculi

It is recommended for cases of minimal fever when antibiotics preceded and followed irrigation The renal function and caliber of the ureter were not damaged by the procedure The pain was usually controlled by codeine The hospitalized patient was able to perform the irrigation with safety and without constant supervision, over a period of several days

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[2] Kelly and Burnam Diseases of the Kidney, Ureter and Bladder Philadelphia D Appleton & Co 1922, vol II, p 208

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LEUKOPLAKIA OF RENAL PELVIS AND URETER

CHARLES C. FALK

Leukoplakia of the urinary tract has long been recognized, but its occurrence in the renal pelvis or ureter has been so infrequent that we should accept every opportunity to obtain a better understanding of this curious tissue response. Since 1882, when Epstein apparently described it for the first time, less than 100 cases involving the renal pelvis and ureter have been presented (McCrea; Keesal and Rosner). It seems worth while to add another case and to review briefly the present concepts of the disease.

Leukoplakia is a metaplastic change in the urinary tract in which the normal transitional epithelium is changed into the squamous or skin-like type, characterized by keratinization and almost always by desquamation. Writers generally agree that the lesion is precancerous.

CASE REPORT

A well developed man of 35, married, and the father of four, employed as a stationary engineer on a logging operation, for the past 15 years had suffered intermittent attacks of colicky pain in the left flank, radiating downward along the course of the ureter. Several urological studies during the past 10 years had failed to reveal the cause of this pain. Meanwhile the attacks were occurring more frequently, and were becoming increasingly severe and incapacitating. He had just had an episode of this pain for about a week. There was no dysuria, frequency, nor hematuria, but he stated that the urine was always cloudy, even in teh interval between the attacks of colic.

The physical examination revealed nothing outside the urinary tract. The urine was grossly hazy, had a pH of 6, a specific gravity of 1.020, and contained neither albumin nor sugar. The sediment showed 15 pus cells per high dry field and many strips and flakes of squamous epithelium. The Wassermann was negative and the blood count entirely normal. Nonprotein nitrogen was 32, and the bleeding and clotting times normal.

The 24F cystoscope was introduced easily and immediately a pearl gray membrane was seen covering almost the entire trigone. The ureteral orifices were not involved, but were somewhat reddened and edematous. On attempting to catheterize the left ureter, an impermeable obstruction was met at 10 cm. above the orifice (figs. 1 and 2). Indigo carmine injected appeared in four minutes, but with poor concentration.

Pyelo-ureterograms revealed several filling defects in the left ureter and an irregular and motheaten appearance. The capacity of the renal pelvis was increased and the terminal calyces were somewhat blunt. The urine from the left kidney showed no acid fast bacilli and the guinea pig inoculation was negative for tuberculosis. Culture of this urine revealed a mixed growth of Escherichia

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27-30, 1953.

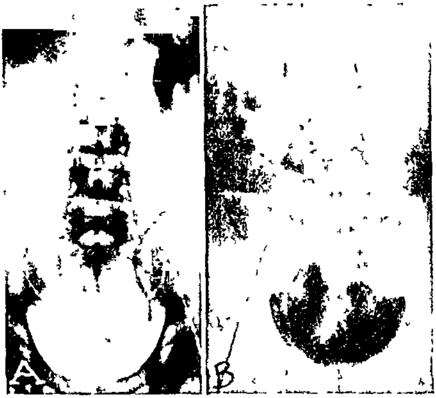

FIG. 1 *A*, pyelo-ureterogram printed in positive showing moderate calyceectasis and pyelectasis; tortuosity of ureter with filling defects *B*, same as *A*, but printed in negative

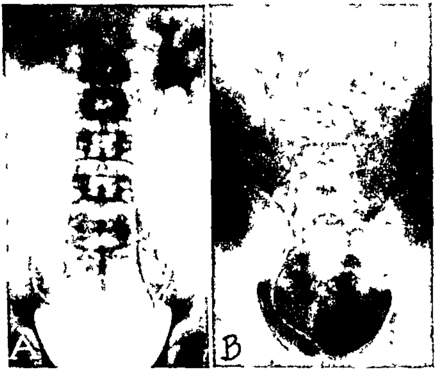

FIG 2 *A*, same as figure 1, *A* except that ureteral catheter is in position to indicate level of impermeable obstruction *B*, same as *A*, but printed in negative (These x-rays are used mainly to point out that urographic findings by means of technique used are not characteristic in leukoplakia)

coli and Staphylococcus aureus. The presumptive diagnosis was made of leukoplakia of the urinary bladder and neoplastic involvement of the left ureter with obstruction to the left kidney.

A ureteronephrectomy was performed The lower ureter, together with a cuff of the bladder, was first excised. The kidney was then removed through the usual lumbar incision. The gross specimens are shown in fig 3. The pathologist, made the following diagnoses: 1) leukoplakia of the renal pelvis and ureter; 2) acute pyelonephritis; 3) cortical cysts of the kidney (fig. 4).

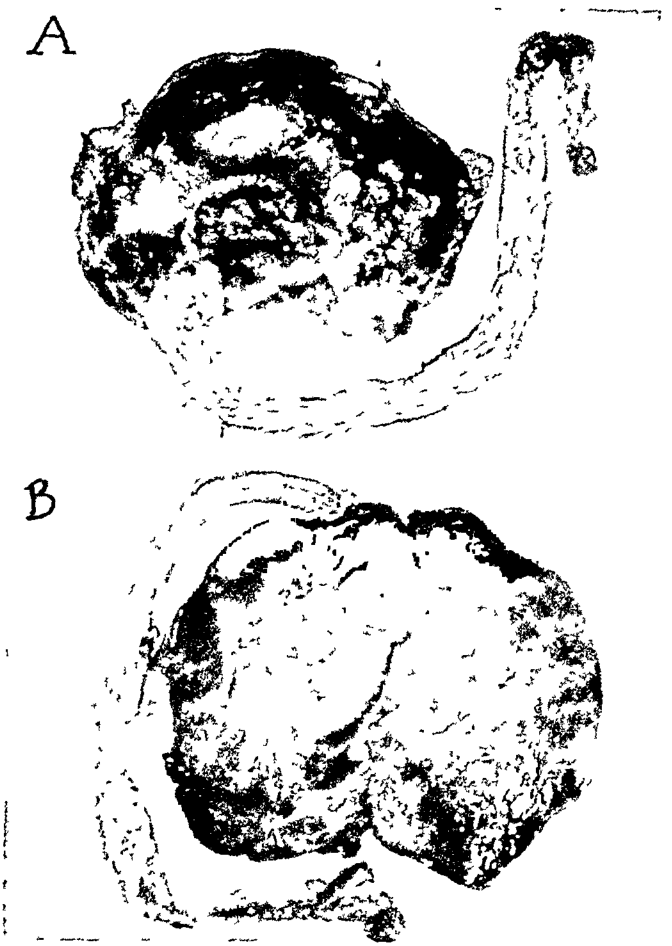

FIG 3. *A*, gross surgical specimen consisting of kidney, ureter and portion of bladder. Ureter has been sectioned longitudinally showing pathologic skin-like structure of upper two thirds of ureter and pelvis. *B*, same as *A* except that kidney and pelvis have been sectioned as well showing extensive involvement which affects entire pelvis.

Recovery was without incident and the patient left the hospital on the twelfth postoperative day. He was examined every 2 weeks for the succeeding 4 months. The pyuria was greatly improved, though the urine continued to be grossly hazy and flakes of epithelium were still present. He regained his original weight in 2 months and had resumed his occupation.

DISCUSSION

The cause of leukoplakia is unknown. Undoubtedly the most widely accepted explanation is that leukoplakia of the urinary tract is a true metaplasia arising as the result of chronic inflammation and irritation, and is the biological process of adaptation to environment in the form of protective cornification (Hinman, Kutzmann and Gibson). In the study of a larger series of cases two uniform observations have been made: 1) pyuria is present in all cases, and 2) leukoplakia usually occurs concomitantly with other diseases. It is suggested, there-

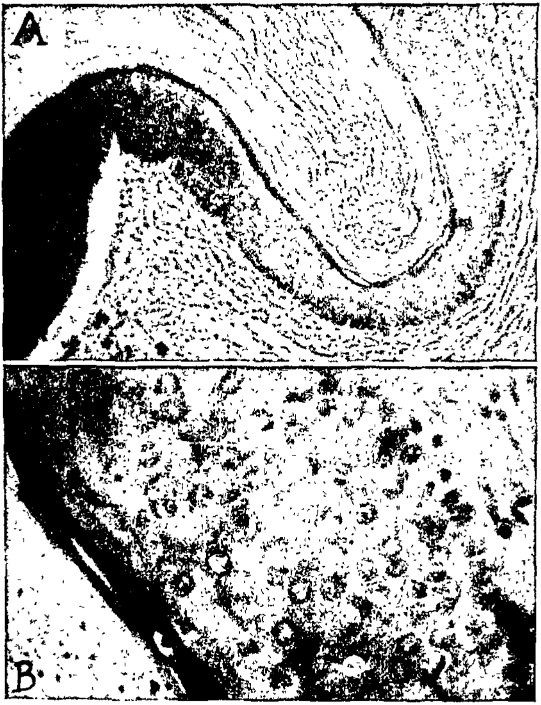

FIG. 4. *A*, cornified stratified squamous epithelium has completely replaced transitional epithelium which normally lines ureter. Note thick layer of desquamated epithelial cells on epithelial surface. H and E stain. *B*, same as *A*, but higher magnification to show cellular details.

fore, that the leukoplakia may be secondary to severe chronic infection, calculous or neoplastic disease, or urinary tract obstruction. It is no longer believed that it is a manifestation of syphilis. While there once appeared to be laboratory evidence that a lack of vitamin A was causative, this view seems to have been abandoned (Senger, Bottone, and Kelleher).

The disease occurs most commonly in the age group between 30 and 50. There are few patients under 20, although occasional cases have been reported in childhood and also in extreme old age. This would lead to the conclusion that any hypothesis that the etiology of the disease is based on embryonal cell rests is untenable. The condition is found about twice as often in the male as in the female (Laughlin and Bilotta).

There are no symptoms typical or characteristic of this condition except as a rule those of the coexisting disease. Frequency, urgency, dysuria, hematuria, any or all may be present. In my patient ureteral colic was the predominant complaint. The outstanding finding noted by several authors is the discovery of cornified epithelium in the urinary sediment. It is described by Senger, Bottone, and Kelleher as the passage of "gritty flakes in the urine." It is also mentioned by Laughlin and Bilotta, and Arnholdt considers it pathognomonic, though he points out that the disease may exist without this finding. It was certainly prominent in the present case.

The difficulty in preoperative diagnosis is evidenced in the cases reported. Subjective symptoms are of little value, and one must re-emphasize the one important objective clue, the finding of large amounts of squamous epithelium in the urinary sediment. This observation should suggest leukoplakia at once. I certainly believe also that if leukoplakia is seen cystoscopically in the bladder, it should be considered possible, or even likely, that the disease may also affect the upper urinary tract. Kretschmer suggested this fact some years ago.

Pyelo-ureterographic findings are certainly not diagnostic in this disease and are only of general value. All writers agree on this point except Arnholdt, who was able to demonstrate, by the use of a dilute medium for pyelography, an x-ray silhouette which he considered consistent with the leukoplakic folds and wrinkles in the mucosa of the kidney pelvis. His description did not apparently impress the later writers.

One author described passing a cystoscopic rongeur into the lower ureter and obtaining a biopsy specimen from which a positive diagnosis was made. While the use of the technique must certainly be limited, its possibility might well be remembered.

Leukoplakia in the upper urinary tract must be differentiated from tuberculosis, neoplastic disease, either squamous or transitional in type, calculosis, severe pyogenic pyelonephritis, and pyelitis and ureteritis cystica and glandularis (Stirling and Ash).

The treatment of leukoplakia involving the kidney and ureter is preferably ureteronephrectomy, both to remove the potential malignancy and to relieve the symptoms. Fortunately in less than 5 per cent of the patients the condition has been bilateral and only conservative palliative measures could be instituted. In the light of our present knowledge such therapy must be directed toward control of infection and promotion of free drainage.

SUMMARY

Leukoplakia of the renal pelvis, ureter, or both, is rare, less than 100 cases having been reported in the last 80 years.

Leukoplakia in the urinary tract is a precancerous lesion.

The etiology is obscure, but the evidence strongly supports the concept that the causative factor is prolonged irritation in the form of chronic infection.

Leukoplakia is usually concomitant with other diseases.

Preoperative diagnosis of leukoplakia of the kidney or ureter is seldom made, but the disease should be suspected when the cystoscopic findings are inconclusive and there are masses of squamous epithelial cells in the urinary sediment.

When leukoplakia can be seen in the bladder through the cystoscope and there is any evidence of disease in the upper urinary tract, the same condition in the kidney and ureter should be considered a strong possibility.

Treatment is ureteronephrectomy when leukoplakia involves the kidney and ureter and is unilateral, as it is in more than 90 per cent of the cases.

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SCHWANNOMAS

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Schwannomas, or, as they are often called, neurinomas or perineural fibroblastomas, arise from the sheath of Schwann, usually from a peripheral nerve. The commonest nerve to be involved is the acoustic nerve.

In reviewing the literature, such a tumor in the retroperitoneal space in close association with the kidney and ureter has not been recorded. The commonest retroperitoneal tumors arising in this region have been reported by Donnelly and Judd. Whether schwannomas in this region have not been recognized or whether they have been confused with the more common tumors such as sarcomas, fibrosarcomas, neuroblastomas, sympathicoblastomas, sarcomas and cystic tumors one cannot proffer an excuse. Frank described a cystic schwannoma containing five or six ounces of clear fluid which arose from low down in the pelvis and had to be differentiated from an ovarian cystic tumor. So far as the literature is concerned, urologists have not before encountered schwannomas which produced urinary tract changes. The authors wish to report two cases of schwannoma, both in female adults, one a solid, relatively benign tumor and the other cystic, with a relatively high degree of malignancy.

CASE REPORTS

Case 1. A white woman, aged 31 (Mrs. E. D., Unit No. C 55562), was admitted to the Urological Service of the New Haven Hospital on April 12, 1951, complaining of a feeling of fullness in the epigastric region for a period of 1 month. She was in the third month of her second pregnancy. She denied any nausea, vomiting or urinary symptoms. She had never had any hematuria. Her family history was irrelevant, and her past history showed good health respective to all systems and one pregnancy which had terminated normally 19 months previously. The family history disclosed that her father died at 66 years of leukemia and asthma and that her mother had been operated upon for a myoma of the uterus. Her general condition was good. Physical examination revealed that the left side of the abdomen was larger than the right. A mass was palpable in the left flank extending from under the costal cage down to the crest of the ilium, smooth in contour, soft in consistency and not particularly tender. The pelvic examination was compatible with the stated pregnancy. Cystoscopic examination showed a normal bladder. The bladder urine was clear in color; pH, 5.5; specific gravity, 1.010; albumin, 0; sugar, 0; microscopic examination showed no pus cells or red blood cells. The urines from the right and left kidneys were normal. Cultures of the urine from each kidney and the bladder were negative for bacterial growth. The renal function test with phenolsulfonphthalein disclosed 25 per cent from the right kidney and 20 per cent from the left kidney in 15 minutes. Bilateral retrograde

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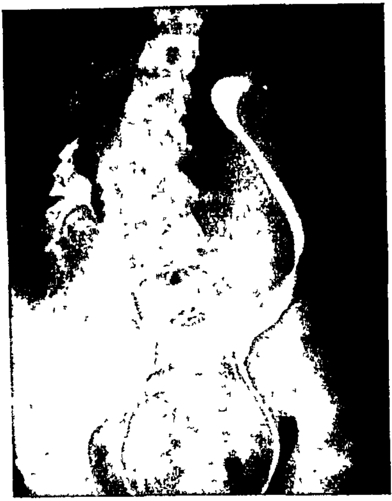

FIG. 1. Case 1. Retrograde pyelogram showing left ureter taking lateral, curved course with dilatation of upper two-thirds. Slight dilatation of pelvis with delicate calyces and high position of kidney.

pyelograms (fig. 1) revealed a normal right kidney, pelvis and ureter. On the left, the ureter took a normal course up to the pelvic brim, swept laterally and posteriorly and returned to the left paravertebral region at the level of the first lumbar vertebra, where the ureter was moderately dilated between the pelvic brim and the renal pelvis. The major and minor calyces of the left kidney were outlined, showed no evidence of dilatation and were less filled than the calyces on the right. The lower and middle calyces were displaced upward and were crowded together as the result of displacement by a large, space-occupying lesion of the lower pole of the left kidney which also displaced the ureter posteriorly and laterally. This large, soft-tissue density showed smooth edges with regular outline and no evidence of calcification and was thought probably to represent an enlarged cyst of the lower pole of the left kidney. The chest x-ray revealed normal bony thorax, diaphragm, heart and mediastinal contents with clear lung fields. The differential diagnosis preoperatively was between 1) retroperitoneal tumor, 2) hydronephrosis of the lower half of the kidney and 3) solitary cyst of the kidney.

Treatment:—On April 17, 1951, the left flank was explored through a lumbar incision. A large tumor shaped like a football was located below the left kidney but not attached to the kidney. Its surface was smooth, solid in consistency and adherent to the posterior abdominal wall and to the descending aorta. The tumor was carefully dissected free and removed. There were not any lymph node involvements. The retroperitoneal space was drained with a cigarette Penrose drain The patient was discharged from the hospital on the eleventh day after operation in excellent condition and with the wound completely healed.

The pathological report of the tumor (fig. 2) removed is as follows:

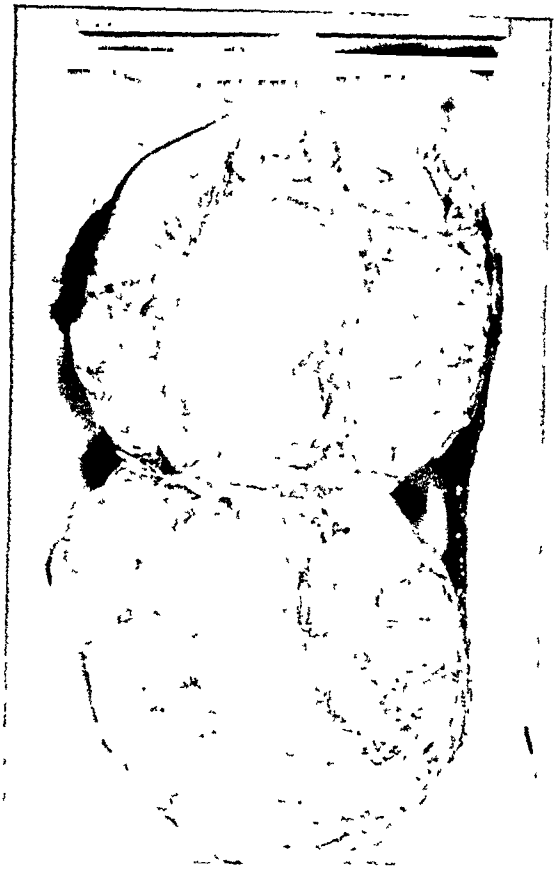

FIG. 2. Case 1. Cross section of solid schwannoma which is well encapsulated

"The tumor is lemon shaped, measuring 17 cm. by 13 cm.; total weight is 1680 gm. Its surface is covered by fascia which can be stripped from the tumor with only slight difficulty, leaving a shiny, yellow and gray glistening surface. The cut surface of the tumor is yellowish-gray in color, soft in consistency and cystic. The microscopic sections show connective tissue containing areas of dense bundles of fibrous-like cells with long, narrow, elongated blue nuclei (fig. 5, *A*). These bundles of tissue seem to interweave, and in some areas the nuclei give the impression of palisading. In other areas loose connective tissue is present. The connective tissue gives the general appearance of having been fatty tissue. In other areas of this connective tissue many round, blue-staining cells are seen which may be chronic inflammatory cells. A large number of small-sized blood vessels are also seen in the tissue. Pathological diagnosis: Schwannoma."

This patient made an uneventful recovery from the operation and 7 months later delivered a normal boy. Six weeks after the operation an excretory urogram revealed slight dilatation of both ureters and pelves, but otherwise the urinary tract was normal.

Case 2. A white woman, aged 33, was admitted to the Urological Service of the Grace-New Haven Community Hospital on November 7, 1948. Her complaints were numerous and varied. She *complained* of vague abdominal discomfort which was not associated with meals. She had bouts of bronchial asthma. Her previous hospital admissions were numerous, and her symptoms were explained on the basis of allergy. Physical examination revealed this patient to have marked scoliosis and lordosis of the thoracic and lumbar vertebrae, a deformity which had been present since birth. Abdominal examination revealed a palpable mass in the left flank, smooth in contour and solid in consistency, which was thought to be a palpable left kidney as a result of displacement caused by the associated scoliosis. The bladder urine was normal, and microscopic examination showed no evidence of pus cells or red blood cells. The urine from each kidney was normal, and the culture from each kidney was negative for bacterial growth. The function of each kidney as measured by the phenolsulfonphthalein test was within normal limits. Bilateral pyelo-ureterograms showed a marked axial torsion of the lower pole of the left kidney caused by a large, well-defined mass below the lower pole of the left kidney (fig. 3). The differential diagnosis was between a tumor of the lower pole of the kidney and a primary retroperitoneal tumor, extrarenal in origin.

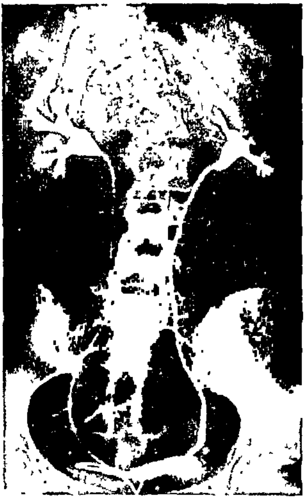

FIG. 3. Case 2. Retrograde pyelogram showing axial torsion of left kidney caused by mass located below kidney and medial deviation of course of ureter.

Treatment:—At operation, a modified left kidney incision was made below and parallel to the twelfth rib and extending towards the umbilicus in a transverse direction. The retroperitoneal space was opened and a large tumor was located extending from the level of the lower pole of the kidney to the crest of the ilium. The tumor was the size of a grapefruit and seemed to be attached medially to the vertebral column. Anterior to it was found a large band of nerve tissue about half an inch in width. The tumor, which was solid in consistency and encapsulated, was excised conserving the kidney.

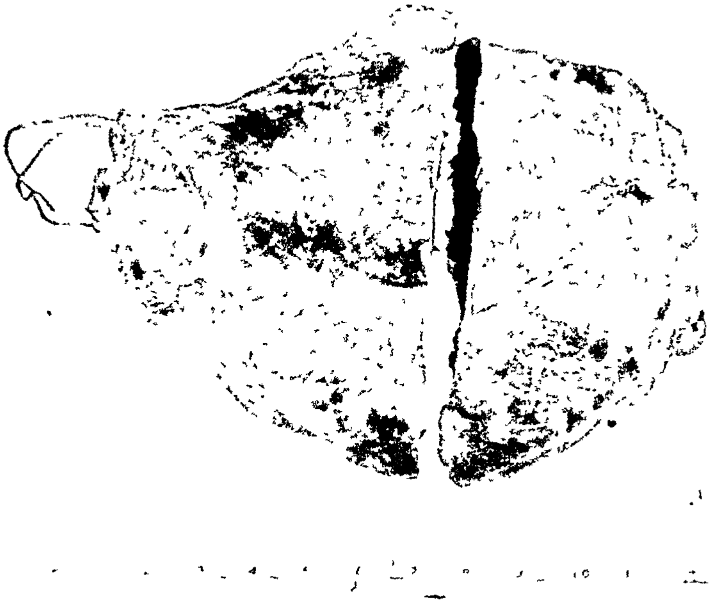

FIG. 4. Case 2. Thick-walled, cystic schwannoma

The pathological report is as follows:

"A thick-walled, cystic tumor (fig. 4), the size of a small grapefruit. The surface is roughly nodular. Cross section of the mass reveals it to be solid with a large area of degeneration and cyst formation. A large nerve trunk issues from one pole of the tumor mass. Microscopic pathological diagnosis: Cystic schwannoma of a retroperitoneal tumor." See figure 5, *B*.

The patient made an uneventful recovery from surgery and was discharged from the hospital 2 weeks later. Three months after the operation she had gained 13 pounds in weight. On July 5, 1949, eight months after surgery, she again began complaining of pain in the left flank accompanied by nausea. She was re-admitted to the hospital on August 18, 1949, complaining of more severe pain in the left upper quadrant of the abdomen accompanied by nausea and vomiting. She had also noted a localized swelling between the eighth and ninth ribs in the left anterior axillary line. Abdominal examination revealed in the left upper quadrant a firm mass measuring about 5 by 6 cm., which did not move with respiration. X-ray study of the chest revealed erosion of the anterior one-third of the left seventh rib at the anterior axillary line and extending from this ragged anterior margin of the seventh rib a large, soft-tissue mass measuring approximately 5 by 7 cm. in diameter. Excretory urograms revealed a normal right kidney, pelvis and ureter. There was no evidence of excretion of dye by the left kidney.

Cystoscopic examination was done, and both ureters were catheterized. Bilateral pyelograms showed failure of the left urinary tract to fill above the fifth lumbar vertebra where a soft-tissue mass could be seen to the left of the vertebral column at the level of the fourth and fifth lumbar vertebrae. The right kidney, pelvis and ureter were normal.

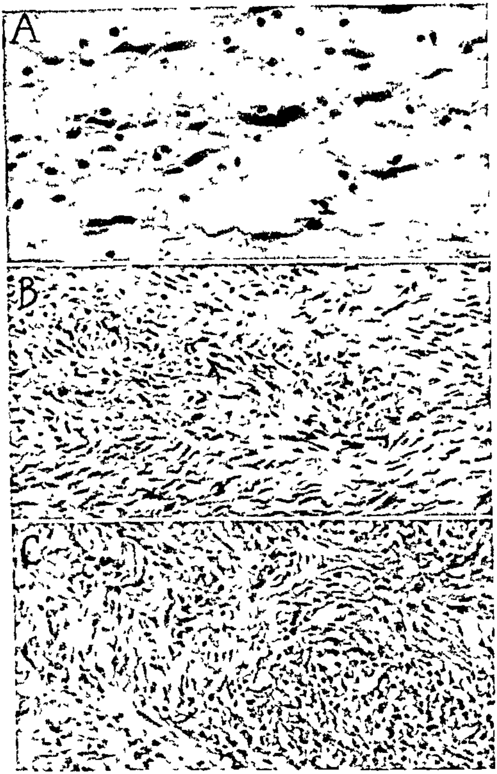

FIG. 5. *A*, case 1 High power, ×350. Dense fibrous-like tissue with elongated nuclei giving impression of palisading with loose connective tissue.

B and *C*, case 2 *B*, photomicrograph, ×250 showing nerve tissue. *C*, photomicrograph, ×250 Nodule from rib showing more active growth of nerve tissue but similar to original lesion.

A biopsy of the lesion on the rib was taken with the following report:

"The specimen consists of two pieces of firm, grayish-pink, gritty tissue each measuring approximately 1 cm. in diameter. Microscopic examination shows whorls of fibrous tissue arranged in irregular patterns. The nuclei of these fibroblasts vary greatly in size, shape and staining reaction and often are large, vesicular and with large nucleoli. A moderate number of mitotic figures are visualized. Diagnosis: Malignant schwannoma (Dr. Levin Waters)." See figure 5, *C*.

The patient expired on October 27, 1949.

PATHOLOGY

There are two types of schwannomas, the benign and the malignant schwannoma. Both of these types are associated with peripheral nerves and are extremely rare in the retroperitoneal space. The malignant schwannoma is often labelled a *fibrosarcoma, but the origin of this tumor is different.* In the main, the above two tumors arise from Schwann cells which have their embryonic origin, the neural crest. The Schwann cells are very active and multiply easily. Tissue cultures have shown that these cells can produce connective tissue fibers. Whenever a malignant tumor arises from the sheath of a peripheral nerve there crops up uncertainty in one's mind as to the embryonic origin of these cells. If this type of tumor arises from mesodermal connective tissue it is called a fibrosarcoma. It is uncertain whether or not the mesodermal element of a nerve sheath can produce a malignant fibrous tissue. The solitary, encapsulated, benign tumor which arises from the sheath of Schwann may be small, solid or large and cystic. The small tumors are solid, but as they grow larger degeneration occurs and cystic formation results. They grow slowly, usually without producing symptoms, although when a large nerve trunk is expanded, pain, paresthesia or other symptoms due to pressure may occur. The solid tumors are benign and are always encapsulated and rarely recur after surgical removal even if the capsule is left behind. It has been questionable whether or not a malignant tumor ever develops from them. Histologically, the microscopic picture is characteristic. Inside the sheath, the tumor tissue is composed of two parts. The cells of Schwann are arranged in twisted bands or cords accompanied by delicate connective tissue fibers. The cells may also be arranged so as to give the appearance of a tactile corpuscle, which is called a Verocay body. Del Rio Ortega, Penfield and Mason have divided the nerve tumors into two types, the fascialar and the reticular. The former consists of an orderly arrangement of parallel and intercellular fibers. The cells may also present transverse parallel ranks separated by nuclear free zones of densely aggregate fibers along with the terminal portions of the cells. The neurilemmoma *consist of a form of* reticular collogen which, however, stains somewhat differently from the fibroblastic collogen. The reticular type shows a disorderly arrangement of a loose meshwork of cells of variable shapes with plentiful intercellular vacuoles or microcytes containing water or mucinoid fluid which stains bluish with benatoxylin. Regimented parallel fibers are not found and collogen fibers are scanty or absent in this type. The two types may be found together. Biologically, they grow slow and are encapsulated. If they are not entirely removed recurrence may develop.

COMMENT

These 2 cases of schwannomas occurred in young adult women and on the left sides. Both were operated upon successfully conserving the kidneys. One tumor was solid and relatively benign, and the other cystic and malignant. It is difficult to state how long these tumors had been present. The former had produced almost no symptoms while the latter had presented symptoms for 10 years. Schwannomas as a rule are relatively benign tumors, although the cystic ones may prove to be malignant. The former patient has remained well for two years, while the latter patient died of general metastatic lesions eighteen months from the time of the operation. Schwannomas are slow-growing tumors and rarely reach more than two centimeters in diameter. The schwannomas in the retroperitoneal space below the renal organ develop into large tumors which compress the ureter and influence its position and function. They are adherent to the posterior abdominal structures, both muscle and vascular tissues. Care should be taken to remove all of the tumor as in all tumor surgery. In the second case, it was more difficult to accomplish complete removal, and, as evidenced by its local recurrence, the tumor was not wholly removed. The widespread metastases indicate the true biological tendency in this one case of disseminating its growth to distant tissues. Neuropathological literature indicates that the tumors may become cystic and malignant, although on the whole they are considered relatively benign.

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PELVIOLITHOTRIPSY IN SURGICAL MANAGEMENT OF STAGHORN RENAL CALCULI

JOHN W. DORSEY

Pelviolithotripsy as the term implies, refers to the fragmentation of the renal calculus through a pyelotomy incision. It is a definite adjunct in the surgical management of certain selected cases, particularly where there exists a low renal reserve, or in the solitary kidney, where nephrolithotomy would be hazardous. The concensus of opinion of such men as Zuckerkandl, Beer, Walters, and Counceller, Robinson, and Priestley favors pyelolithotomy over nephrolithotomy as the safer of the two procedures. The reports of Priestley and Dunn, and Prince, Scardino and Presti indicate that surgical removal of staghorn calculi is preferable to medical management.

In reviewing the literature we have not encountered an article that discusses fragmentation in detail. Simple fracture through the body of a staghorn calculus will often permit the atraumatic removal of the two fragments through a pyelotomy incision.

The Bigelow lithotrite was chosen because the blades are long and slender, and more easily introduced into the pelvis, and yet have great crushing power. The even, steady application of force obtained through the screw mechanism permits shearing the calculus into two major fragments without pulverizing it. The screw mechanism in contrast with the pistol grip type eliminates any sudden jerk at the time of fragmentation that would prove injurious to the kidney.

No attempt will be made to discuss the etiology; preoperative selection of cases for surgery; or postoperative medical management, as the literature is replete with excellent articles dealing with these subjects.

SURGICAL TECHNIQUE

The kidney, renal pelvis, and proximal ureter are completely mobilized by a combination of blunt and sharp dissection performed through an adequate lumbar incision. The posterior aspect of the pelvis is more completely visualized by elevating the renal hilum with vein retractors in the manner described by Walters, Counseller and Priestley. An elliptical incision (fig. 1, *A*) is then made in the renal pelvis extending from the superior to the inferior border on the posterior aspect with the convex curve directed toward the renal hilum. The posterior flap of renal pelvis is then peeled off the projecting pelvic portion of the staghorn calculus (fig. 1, *B*) and the pelvis is then gently retracted anteriorly. The calculus is then manipulated carefully and extracted if possible. In some instances because of close approximation of calculus to pelvis it is necessary to pass a curved hemostat around the pelvic portion of the calculus at the hilum in order to permit the introduction of the blades of the lithotrite. The female blade of the Bigelow lithotrite is introduced into the space between the anterior surface of the calculus and the pelvic mucosa; the male blade is then introduced

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on the posterior aspect (fig. 1, *C*). The most desirable plane for cracking the calculus as determined by preoperative x-ray studies is attained by gentle manipulation of the lithotrite. In the cases reported the calculus was sheared into two major fragments which were readily extracted through the pyelotomy incision. Small calculi may then be removed with stone forceps or scoop. In the presence of a dilated calyx with narrowed infundibulum the small calculi may be removed through a small, stab type nephrotomy incision as in case 2. Where a bulbous projection of the staghorn calculus is locked in a minor calyx it will be necessary to perform a small nephrotomy incision and fracture the calculus at the level of the constricted infundibulum. An x-ray study of the kidney is then made to determine if any radio-opaque calculi have been overlooked. The calyces are lavaged in an attempt to evacuate any nonradio-opaque calculi or debris that would act as a nidus for recurrent calculus formation.

An 18F bulb catheter, and two 5F ureteral catheters are introduced simultaneously into the renal pelvis through an inferior calyx (fig. 1, *D*). The balloon is distended with 3 cc of water, and left as a nephrostomy tube. The two ureteral catheters are advanced into the ureter 15 to 20 cm., and act as a splint. The elliptical pyelotomy incision is closed with interrupted 000 sutures of plain cat-

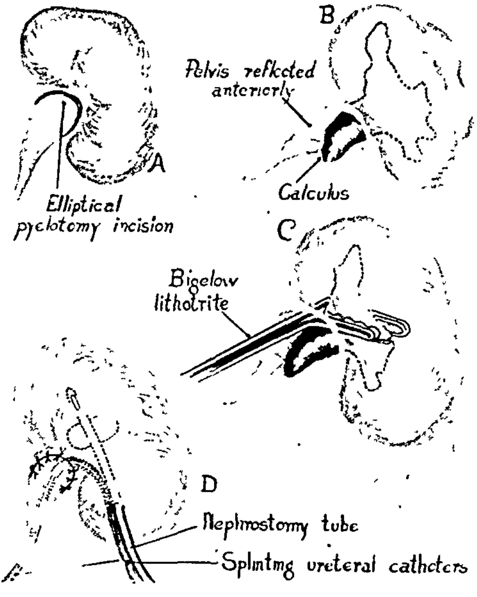
A
Elliptical pyelotomy incision
B
Pelvis reflected anteriorly
Calculus
C
Bigelow lithotrite
D
Nephrostomy tube
Splinting ureteral catheters

FIG. 1 Semidiagrammatic illustration of surgical technique. *A*, pyleotomy incision. *B*, reflection of pelvic flap. *C*, introduction of lithotrite. *D*, closure.

gut, no attempt being made to obtain a water tight closure. The kidney is suspended in favorable position beneath the twelfth rib, by Kelly triangular sutures. Gerota's fascia is approximated to the quadratus lumborum muscle with interrupted 00 chromic sutures in a modified type of Deming nephropexy. The region around the renal plevis is left open to permit favorable drainage. A Penrose drain is introduced into the parapelvic area posterior to the lower pole of the kidney, and a second drain along the mobilized portion of the ureter. The incision is closed in layers, and the nephrostomy and splinting ureteral catheters fixed to the skin with 0 silk sutures.

POSTOPERATIVE MANAGEMENT

The nephrostomy tube is irrigated only if definite impairment of drainage is evident. The balloon is decompressed in 48 hours. Solvent solutions are not used in the immediate postoperative phase, feeling that their irritant action outweighs their usefulness. Beginning at 72 hours the ureteral catheters are withdrawn 1 to 2 cm. daily. The Penrose drains are left undisturbed until there is a marked dimunition in drainage, then they are shortened daily. Ambulation is inaugurated on the fifth to seventh postoperative day, pelvic circulation having been stimulated previously by passive exercise of the lower extremities at frequent intervals.

The immediate medical management consists primarily of adequate supportive measures; hyaluronidase 150 TR units (Wydase) daily; and appropriate antibiotic therapy. The accepted methods for the prevention of recurrent calculus

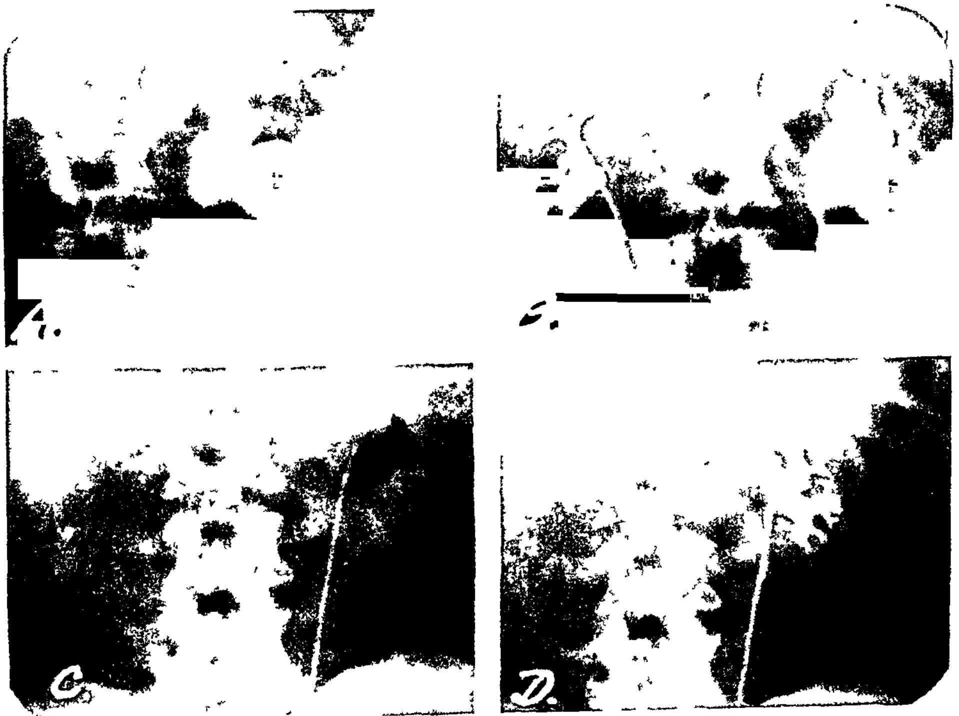

FIG. 2. Case 1. *A*, preoperative scout film. *B*, retrograde pyelogram *C*, fifteen months' postoperative scout film. *D*. retrograde urogram

formation are utilized after the patient has completed his postoperative convalescence.

CASE REPORTS

Case 1. Mr. F. L., aged 51, was seen because of two bouts of right flank discomfort. A scout film and retrograde urogram (fig. 2, *A* and *B*) revealed a small calculus lodged in an inferior minor calyx of the right kidney, and a left staghorn renal calculus. Indigo carmine appeared from the right kidney in 4 minutes, and from the left kidney in 10 minutes. Urine recovered from each kidney was sterile on culture, and blood chemistry studies were within normal limits. The right renal symptoms promptly subsided. The staghorn calculus was then removed in the manner described. The two major fragments (fig. 4, *A*) were easily extracted through the pyelotomy incision without evident trauma to the renal parenchyma.

Convalescence was uneventful. The voided urine has been sterile since the twenty second postoperative day. A scout film and retrograde urogram (fig. 2, *C* and *D*) made 15 months following surgery revealed no recurrent calculus formation, and an excellent return to normal of the calyceal system. The right renal calculus has remained stationary in size and asymptomatic.

Case 2. Mrs. K. R., aged 62, had a right nephrectomy performed 15 years previously for calculus pyonephrosis, at which time a small calculus was present in the left kdiney. In recent years she had noted mild, recurrent, left flank discomfort. The scout film and excretory urogram (fig. 3, *A* and *B*) revealed a large

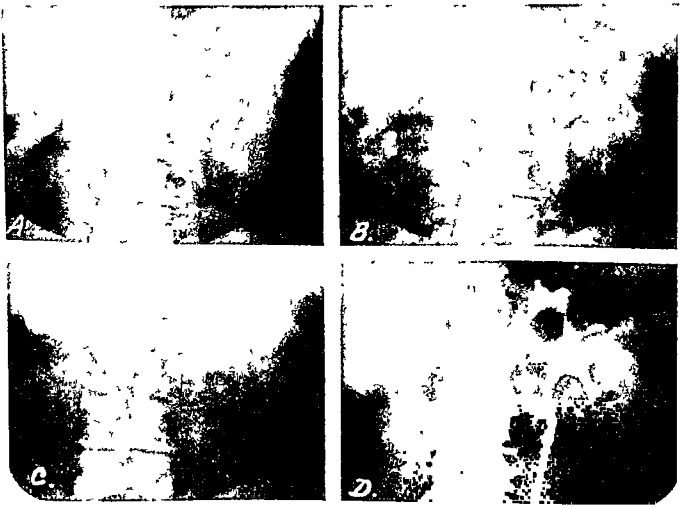

FIG 3 Case 2 *A*, preliminary scout film *B*, excretory urogram *C*, three months' postoperative scout film *D*, retrograde pyelogram

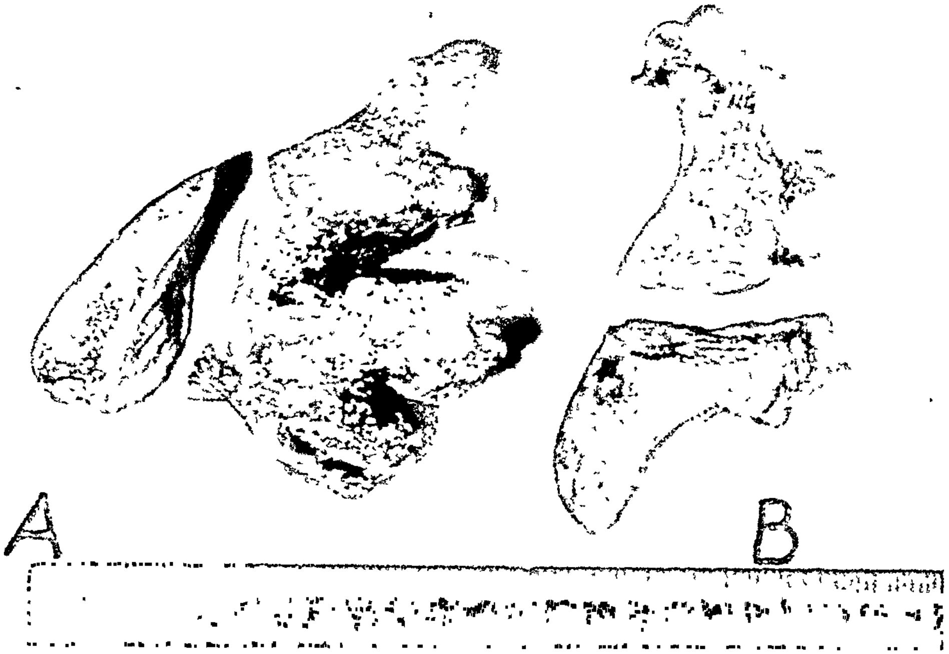

FIG. 4. Surgical specimens. *A*, case 1. *B*, case 2

staghorn calculus, and several smaller calculi in the solitary left kidney. The superior group of calyces appeared to be involved in a localized hydronephrotic change. The general condition of this patient was excellent; blood pressure 160 systolic and 90 diastolic; blood chemistry studies were within normal limits, and Gram's stain of the urinary sediment, negative for organisms.

At surgery the calculus was found to be in such close approximation with the pelvic mucosa that it was necessary to free it in the manner previously described, before the blades of the Bigelow lithotrite could be introduced. Figure 4, *B* shows the calculus sheared into two major fragments. Within 30 minutes following surgery the kidney was secreting relatively clear urine, and at no time was urinary suppression noted. The maximum elevation of nonprotein nitrogen was 42 mg. per cent.

Three months later the nonprotein nitrogen was 21.5 mg. per cent. The scout film and retrograde urogram (fig. 3, *C* and *D*) reveal no recurrent calculus formation, and a definite regression in the previously noted hydronephrotic changes. Repeated cultures of the urine have been sterile. The patient has been leading a fully active, comfortable existence.

DISCUSSION

Meticulous care in handling the kidney with low renal reserve during mobilization coupled with the atrumatic removal of the staghorn calculus tends to reduce to a minimum the likelihood of immediate postoperative urinary suppression. The use of the elliptical pyelotomy incision is very important. It permits the reflection of the pelvis and ureteropelvic junction out of the field of manipulation, and in contrast with the longitudinal pyelotomy incision there is no tendency for extension of the incision to involve the ureteropelvic junction with subsequent stricture formation This incision permits greater accessibility in manipulating the calculus, and thus facilitates the introduction of the blades of the lithotrite Due to the adequacy of the pyelotomy incision, digital palpation and instrumental removal of small calculi is simplified Closure is simple, and being located at the widest portion of the pelvis there is less likelihood of distortion by scar tissue

The shearing affect of the Bigelow lithotrite is evidenced by the surgical specimens (fig 4, *A* and *B*).

It is mandatory to correct any ureteropelvic junction obstruction at the time of surgical removal of the calculus

The two splinting ureteral catheters maintain the ureter and ureteropelvic junction in good alignment, and permit constant ureteral drainage of the renal pelvis The nephrostomy tube allows immediate drainage, and may be left in situ as a permanent method of drainage if the situation so demands Nephropexy, further enhances a favorable alignment of ureter and pelvis, and facilitates the change of nephrostomy tubes if this be necessary The parapelvic drains are left relatively undisturbed to prevent pooling of urine seeping from the pelvic incision, which would predispose for scar tissue formation and subsequent obstructive uropathy X-ray control at the time of surgery is of the utmost importance

The two cases reported fulfill the tenets laid down by Hess for obligatory, conservative renal surgery We believe that the favorable response to surgery in these two cases was due primarily to the relatively atraumatic method of removing the calculi

SUMMARY

The technique of pelviolithotripsy utilizing the Bigelow lithotrite is described and the use of this method of surgical management in selected cases of staghorn renal calculi advocated

The posterior elliptical pyelotomy incision is described and the many advantages of this incision discussed

Two cases of staghorn renal calculi requiring obligatory, conservative surgery are reported wherein this technique was utilized with favorable results

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SPONTANEOUS DISSOLUTION OF RENAL CALCULI

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Although rare, the spontaneous dissolution of renal calculi does occur. The literature on this subject was reviewed by Sisk and Bunts in 1935 and by Lassen in 1939. McCrea and Van Buskirk reported a single case in 1951. Despite these reports, the significance of this phenomenon seems to have been overlooked.

REVIEW OF LITERATURE

Scheele, in 1924, observed marked reduction in size of four renal calculi in a woman aged 34 over a period of 4 years. Hellström, in 1925, describing three patients, noted the spontaneous disappearance of a large recurrent calculus in the right kidney over a period of 5 years in a woman 24 years of age. A second and similar case was observed to occur over a 4-year period in a woman aged 26. Bilateral calculi were found to have disappeared in a man aged 45 over a period of 8 years. In this patient stones apparently developed during convalescence from a fractured femur. Hasselström reported almost complete disappearance over one month's time of a large renal calculus in a woman aged 40. This patient also suffered from a gastric ulcer. Nadeau, in 1934, reported the disappearance of several calculi in a solitary kidney over a period of 6 months. This patient was a nurse who drank a gallon of distilled water daily. Kearns, in 1935, reported the dissolution of a large renal calculus in a woman aged 42 over a period of several months. This patient disliked to drink liquids with the exception of beer. Barney reported the spontaneous dissolution of bilateral renal calculi in a male aged 22 over a period of about 3 months. The stones apparently developed during immobilization for fracture of the femur. Sisk and Bunts reported the complete dissolution of bilateral renal calculi in a female child aged 13 over a period of a few months. This patient had been ill with coxitis prior to discovery of her calculi. Lassen reported the disappearance of bilateral renal calculi in a woman aged 17 over a period of one year. This patient had been immobilized for disease of the hip joint prior to development of her stones. Wesson, in 1950, reported the case of a 21 year old male who was found to have bilateral renal calculi, one a staghorn, in the course of convalescence from a fractured femur. These stones underwent complete dissolution over a period of about 6 weeks. The patient was given an acid ash diet and ammonium chloride. McCrae and Van Buskirk, in 1951, reported one case of spontaneous dissolution of bilateral renal calculi which were apparently stones of recumbency. Gibson reported the following case in 1937. The patient, a man 48 years of age, came to the Southern Pacific Hospital suffering with renal colic. Urologic investigation revealed large bilateral renal calculi of the staghorn type associated with chronic pyrlonephritis. Since function was most impaired on the right, a nephrolithotomy was done on that side. The patient was then sent home to recuperate, with instructions to return

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within a month for operation on the left kidney. He did not return for 4 years. Investigation then showed that the large staghorn calculus in the left kidney had apparently disappeared spontaneously. The pyuria had likewise cleared up, and there was no evidence of recurrence on the right side. During these 4 years the patient had been under no dietary regimen or treatment of any kind. On his own initiative, he had for one year drunk a daily cup of tea brewed from horsetail grass.

CASE REPORTS

Case 1. In March 1951, a 75-year old man was admitted to the Stanford Service of the San Francisco Hospital with a complaint of prostatism. He was found to have an advanced carcinoma of the prostate and was placed upon stilbestrol by mouth. X-rays revealed the presence of an asymptomatic large left renal calculus. Because his general condition was poor, operation was not advised. Four months later, follow up x-rays disclosed the complete disappearance of the calculus. No treatment had been given for the calculus and the patient passed no stones. (See figure 1.)

Case 2 is reported through the courtesy of Dr. Emmett Henderson. A young woman, aged 23, was seen in May 1949. She complained of pain, of 1 week's duration, in the left renal area. She had previously been in good health. Excretory urograms disclosed a calculus obstructing the left ureteropelvic junction. The patient was advised to enter the hospital, but refused. She returned 1 month later at which time excretory urography showed no evidence of a calculus, and retrograde pyelograms were normal. No treatment had been given, and the patient had passed no calculi. (See figure 2.)

Case 3 is reported through the courtesy of Dr. Jack Lynn and Dr. R. H. Greeley. A 39 year old woman was first seen in April 1948 because of pain in the left renal area. She gave a past history of bilateral nephrolithotomy 4 years previously. Examination disclosed an acutely ill woman with tenderness over the

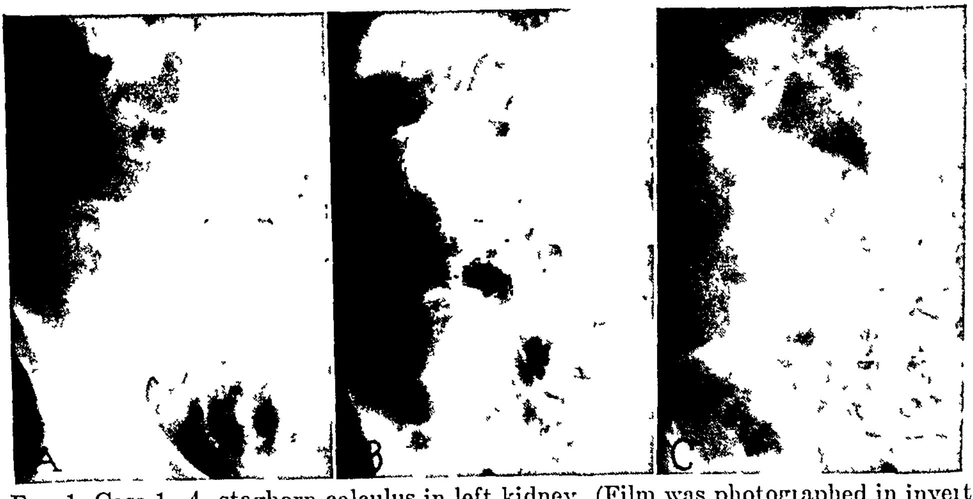

FIG. 1. Case 1. *A*, staghorn calculus in left kidney. (Film was photographed in inverted position showing calculus to be apparently in right kidney.) *B*, another view showing staghorn calculus in left kidney. *C*, film taken 4 months later showing disappearance of calculus.

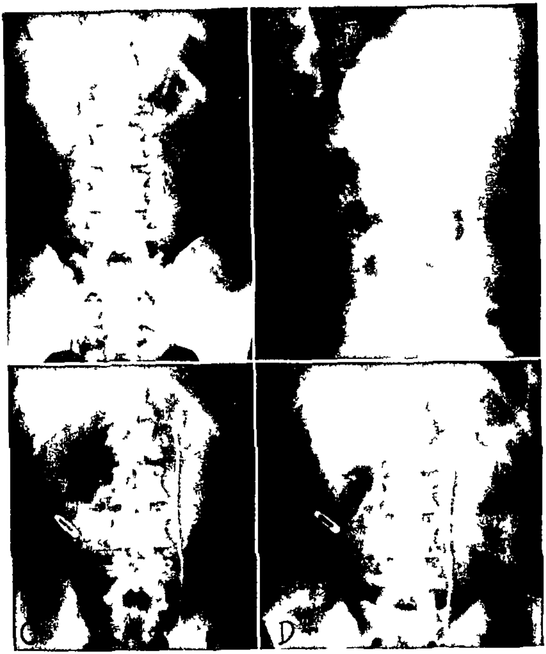

Fig 2 Case 2 *A*, excretory urogram showing calculus at left ureteropelvic junction, and suppression of function on left *B*, lateral view showing calculus *C* and *D*, films taken 1 month after *A* and *B* showing disappearance of calculus

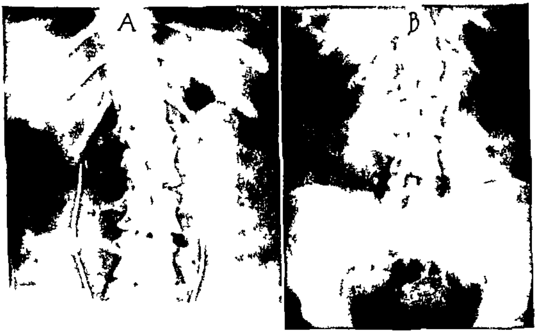

Fig 3 Case 3 *A*, plain film with catheters showing large calculi in lower pole of each kidney and calculus in upper left ureter adjacent to tip of catheter Calculus adjacent to catheter on right and superlateral to transverse process of left lumbar vertebra was in isolated calyx and not in pelvis or ureter *B*, film taken 8 months later showing almost complete disappearance of large calculi in both lower poles One calculus on right remains unchanged similar calculus persists on left side

left kidney, gross pyuria, and a nonprotein nitrogen of 103 mg. per cent. Retrograde pyelograms disclosed bilateral calculi in the lower pole of each kidney and a stone at the ureteropelvic junction of the left kidney. A diagnosis of chronic bilateral pyelonephritis was made and Pseudomonas aeruginosa was cultured from the urine. The patient was treated with antibiotics, a low phosphorus diet, and amphogel. Over a period of several months, the urine showed a pH of 6.0–6.5, a specific gravity of 1.002 to 1.010 with 2 plus albumin, and persistent pyuria. Eight months after her initial visit, x-ray examination disclosed an apparent disappearance of the calculus in the left uretero-pelvic junction, and marked diminution in size of the renal calculi in the lower pole of each kidney, only small fragments remaining. (See figure 3.)

Case 4. Although details of the case are unavailable, the late Dr. Clark Johnson observed a patient in whom a large staghorn calculus spontaneously decreased to about one-fourth its original size.

DISCUSSION

Although one of the reported cases was treated with a large water intake, one patient was given acidifying drugs and an acid ash diet, one patient drank large quantities of beer and little else, one patient was given stilbestrol, and one was given a low phosphorus diet and amphogel, none of these measures has consistently resulted in the successful planned dissolution of renal calculi. Until much more is known as to the mechanism of dissolution of calculi, the phenomena reported here must be considered as essentially spontaneous and due to unknown factors.

The fact that spontaneous dissolution can occur is of great significance in two respects: 1) It suggests that dissolution by medical treatment is a possibility. Additional knowledge of the physico-chemical factors involved in the formation and dissolution of calculi is needed before this can be accomplished. 2) It throws some additional light on the role of urinary colloids in relation to calculus disease.

Protective colloids in normal urine have been held responsible for keeping in suspension the sparingly soluble salts which constitute urinary calculi. The recent articles by Butt, et al., concerning the use of hyaluronidase make use of this theory as a basis for their claim of success in using this material to treat urolithiasis.

In view of the foregoing, it might be wise to consider some simple facts regarding the known physico-chemical activity of colloids.

The word "colloid" refers to a state of subdivision of matter and not a special kind of matter. In general, colloidal particles are larger than molecules but submicroscopic, ranging from one half micron to one millimicron in diameter. Ordinary suspensions settle out on standing, but colloidal suspensions remain suspended. The colloidal particles are sufficiently fine so that the Brownian movement overcomes the force of gravity. Thomas Graham, in 1862, observed that solutions of certain substances such as proteins, polysaccharoses, gums, etc., did not diffuse through parchment and other membranes as readily as sugars, salts, and other materials which crystallize. He called these substances colloids from the Greek word for glue. The crystalline substances which diffuse readily through membranes, he called crystalloids. We now know that many typical colloids such as certain proteins are crystallizable, while practically all crystalloids may, under proper conditions, be brought into the colloidal state.

The biologically important colloids are hydrophilic or "water-loving." That is, they have a great affinity for water and readily form stable solutions or gels. Examples of these are albumins, soaps, gums, tannins, starch, gelatins, glue, proteins, and complex carbohydrates. Suspensoids or lyophobic colloids include colloidal solutions formed by metals, inorganic salts, etc. There is no affinity between these particles and water. They are flocculated by very small quantities of electrolytes, and when so precipitated, cannot ordinarily be brought back into colloidal solution. The precipitation of suspensoids is therefore irreversible.

A "protective colloid" is one which will cause the finely divided particles of a suspensoid to remain in suspension whereas, in the absence of the protective colloid, the particles would settle out of the solution on standing. An example of this is the photographic dry plate. Silver chloride is formed from its ions in a solution containing gelatin. The gelatin coats each particle of silver chloride and prevents precipitation. Protective colloids will cause insoluble salts to remain in suspension but will not stop the formation of insoluble calcium oxalate and calcium phosphate, although it could hinder their precipitation and settling out of solution. Nor would the addition of a protective colloid cause a solid precipitate such as calcium oxalate or calcium phosphate to become resuspended.

From the foregoing, it would seem evident that although protective colloids may hinder the precipitation or settling out of insoluble salts in urine, they would not stop the formation of the insoluble salts from their ions or cause the solution of precipitates or solid calculi, unless they behave as crystalloids and *enter into actual chemical combination with the insoluble material.* Thus, it is apparent that protective colloids, as such, in urine could not be responsible for the spontaneous dissolution of urinary calculi.

The only rational explanation for the spontaneous dissolution of renal calculi is that a change in chemical equilibrium in the urine has occurred which favors solubility of the salts composing the stones. Whether this occurs in the case of calcium stones by 1) a decrease in the concentration of calcium, phosphate, carbonate, or oxalate ions in the urine, 2) by reduction of the pH of the urine, 3) by the increased excretion of substances forming soluble complexes with calcium, or 4) by any or all of the above plus the excretion of a catalyst to speed the reaction, is as yet unknown.

SUMMARY

Thirteen cases of spontaneous dissolution of renal calculi have been found in the literature. Three cases are reported here and one other case is known to have occurred. Of all these cases, five were apparently stones of recumbency, and two patients suffered from chronic pyelonephritis. It seems likely that spontaneous dissolution of renal calculi occurs more commonly than one might suspect from the literature.

Spontaneous dissolution of renal calculi is significant because 1) it suggests that the medical dissolution of calculi may be a possibility, with increased knowledge and 2) this phenomenon can be explained only on the basis of a change in chemical equilibrium in the urine favoring solubility of the salts composing the calculus, and 3) an increase in protective colloidal material in urine will not alone cause the dissolution of renal calculi.

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CLINICAL MANAGEMENT OF RENAL LITHIASIS WITH HYALURONIDASE

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This presentation is an analysis of the clinical results obtained by using hyaluronidase for control of renal calculus formation in 36 patients Particular emphasis is directed toward indications for hyaluronidase therapy, determination of proper dosage, and contra-indications to usage of this drug The physico-chemical mechanism by which parenteral administration of hyaluronidase increases the protective urinary colloids and aids in the prevention of renal calculi has been reviewed previously [1-7]

Clinical, laboratory, and x-ray procedures usually employed for investigating patients with stones are carried out, with the exception that cystoscopic examinations and retrograde pyelo-ureterograms are not performed if it is possible to obtain all necessary information without these measures Bleeding or exudate formation may nullify the accuracy of the protective urinary colloid determinations Excretory radiographic studies are routinely made when renal function is adequate

The effect of hyaluronidase on urine may be conveniently followed in a series of uncentrifuged specimens, taken before and during hyaluronidase therapy, and allowed to settle for one hour at room temperature [1] In such a series, the turbidity and sediment usually begin to diminish in specimens voided about 30 minutes after the injection When turbidity increases in successive 1 hour specimens, another dose of hyaluronidase is needed If no decrease in turbidity and sediment is observed, the dose of the enzyme should be increased As a supplement to this testing procedure, the response may also be studied by computing the rate of formation of deposits on the glass connecting tip attached to indwelling catheters during alternate periods with and without hyaluronidase injections This effect is most pronounced in nephrostomy drainage tubes and least in bladder catheters with intermediate effectiveness in ureterostomy catheters

Reduction in surface tension of urine closely correlates the clearing of tur-

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bidity and sediment if these are present initially. Tensiometric determinations are of greatest value when the urine is initially clear with no sedimentation. We have found that the average surface tension of urine in white males and females is 65 and 60 dynes per centimeter respectively.[5, 8] Following injection of sufficient dosage of hyaluronidase, the surface tension decreases from 8 to 14 dynes per centimeter within 30 minutes to 2 hours and remains decreased as long as the effect of hyaluronidase is being maintained.

The lyophilized hyaluronidase is reconstituted with sterile saline rather than with distilled water. To the vial containing 1500 turbidity reducing units (T. R. units), 10 cc or 5 cc of saline are added with aseptic precautions to provide a solution containing 150 or 300 T. R. units per cubic centimeter respectively. The latter concentration is convenient when the larger doses are required. When prepared with strict aseptic precaution, such solutions are stable without refrigeration for 2 weeks. If the hyaluronidase is in standardizing units, other than turbidity reducing units, their relation to the other must be determined. For example, 500 viscosity units are approximately equivalent to 150 turbidity reducing units. In all cases, the subcutaneous injection site should be rotated. If local infection develops, as in patients instructed to use hyaluronidase at home between office visits, the infected site should be avoided. Needles of 25 G and ⅝ inch are recommended.

Observations to date indicate that patients vary widely in the quantity of hyaluronidase required to clarify pathologic cloudy urines, and the dosage must therefore be determined individually. In approximately 80 per cent of the cases, clarification of the urine occurs after subcutaneous doses of 300 to 600 turbidity reducing units of hyaluronidase. The urine response to suitable doses of hyaluronidase is rapid and easily ascertained. This usually occurs within 30 minutes to 2 hours after injection. The dosage requirements are greater in the presence of infections, such as those due to P. aeruginosa and streptococci, or to urea-splitting organisms, particularly staphylococcus or Proteus. In such cases, dosages as high as 900 to 1800 T. R. units every 24 hours may be indicated. Also "split" dosages, i.e., 600 to 900 T. R. units every 12 hours may be necessary to keep the urine free of sediment.

Contra-indications to hyaluronidase therapy are hypersensitivity to the drug and impaired renal function. The highly purified enzyme used in our studies has little tendency to produce allergic reactions. In over 900 of our patients who have received injections of hyaluronidase, only three had significant localized urticaria and 2 of these were later treated without reaction. In one of the patients a different brand of hyaluronidase was administered and no reaction occurred. Desensitization to the drug has not been attempted since the injections can usually be resumed without further sensitivity response after a rest period. Also we have observed that inadequate dosage of hyaluronidase may be dangerous, due to the fact that "sensitization" of urinary crystals may occur with acceleration of stone growth. If clarification of the urine does not develop within 6 to 8 hours on the dosage outlined above, the treatment should be discontinued.

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The treatment of severe calculus disease by hyaluronidase demands day to day control. The management should be carried out considering stone as a constitutional as well as a local disease. Hyaluronidase therapy should be considered adjunctive, as all other forms of treatment usually employed are instituted. Metabolic disorders are corrected, if possible. Antimicrobial drugs and urologic measures are employed according to usual indications. If the stone is phosphatic, we prescribe Basaljel, two tablespoonsful after meals and at bedtime. This dosage is well tolerated and causes a reduction in urinary phosphate excretion. Appropriate dietary measures are instituted and large doses of vitamin A are prescribed in all stone cases.[7] Each patient is urged to maintain a daily urine output of approximately 3000 cc. In short, every measure is utilized which promises to assist in minimizing formation, growth or recurrence of stone.

During the past 30 months, we have observed 311 patients with renal lithiasis. Of this number, 54 were selected for hyaluronidase therapy because they showed a marked tendency to formation of renal calculi and because conditions were favorable to enhance the rate of stone growth. The cases of patients who had followed the regimen for less than 20 months were excluded from this series, as they would not seem to provide a substantial test of therapeutic efficacy. Thirty-six of the 54 patients have been on hyaluronidase therapy for periods ranging from 20 to 30 months, average 23 months. In these patients, no previous forms of therapy had been effective in reducing formation or growth of stones. Twenty of the patients had previously undergone one or more operations for stone, nine of which were nephrectomies. Ages ranged from 13 months to 78 years. There were 20 males and 16 females. All of the patients were white.

For control, the clinical course of the 36 patients before institution of hyaluronidase therapy was used. We fully realize that this did not provide a completely reliable basis for comparison. Estimation of the time interval between the first knowledge of presence of stone and institution of therapy was often difficult and possibly inaccurate. Chemotherapeutic and antibiotic preparations were fewer and less readily available during the pre-treatment (control) period, although in most cases sulfonamides and penicillin had been used. Some had received streptomycin, aureomycin, terramycin and chloramphenicol. All of the selected 36 patients followed the therapy reasonably well, although the regimen was not strictly adhered to in every case and deviations were demonstrable on an objective basis. In fact, some deletions of therapy provided the most impressive exhibition of the effectiveness of the program. Three patients discontinued the drug for periods of 8 weeks, 9 weeks and 17 weeks respectively. In these patients, stone formation had been controlled while taking hyaluronidase and after discontinuing the drug there was rapid increase in size of existing stones.

As a result of our earlier observations concerning the responsiveness of certain types of renal calculus formation to hyaluronidase therapy, the 36 patients in this series were classified into group A and group B. Group A included 15 patients with multiple, small, calyceal or other small calculi, rapidly forming in a solitary kidney or in both kidneys. From the case histories, laboratory and x-ray findings, these were considered to be primary stones which we now believe to be caused by innate or acquired deficiency of protective urinary colloid. Group B included 21

TABLE 1. *Summary of results following administration of hyaluronidase for renal lithiasis*

GROUP	STONE FORMATION CONTROLLED	STONE FORMATION SLOWED	STONES SMALLER AND LESS DENSE	STONE FORMATION NOT CONTROLLED
A—15 cases	9 (60.00%)	3 (20.00%)	1 (6.67%)	2 (13.33%)
B—21 cases	7 (33.33%)	7 (33.33%)	1 (4.77%)	6 (28.57%)

patients with large stones or large and small stones in a solitary kidney or in both kidneys. These were considered to be secondary type stones or secondary stones superimposed on an original primary stone as a nucleus. These stones resulted from stasis and infection, hyperexcretion of crystalloids, recumbency, hyperchloremic acidosis, or other known factors.

Results (table 1) were graded: 1) control of formation or growth of stone and no passage of stone; 2) reduction in rate of development and growth of stone as compared to previous calculogenesis; 3) diminution in size and density of stones; 4) failure to arrest or retard development and growth or passage of stone. Roentgenograms were made every 60 to 90 days on all patients in this series.

Group A: In 11 of the 15 patients, stones were available for analysis. Nine were composed of calcium oxalate or calcium oxalate and apatite and one each of cystine and uric acid. The last two named types of stone were not demonstrated by x-ray, but cystine and uric acid calculi were frequently passed and recovered for analysis. Urine culture was negative for growth in 13 of the patients; B. coli was present in one; Staphylococcus aureus, non-urea splitting, was present in one. Patients in group A generally required smaller doses of hyaluronidase than those in group B. Three required 150 T. R. units every 24 to 48 hours; 9 required 300 T. R. units every 24 hours; 3 required 600 T. R. units daily.

Group B: In 7 of the 21 patients, stones were available for analysis. Five were composed of apatite and ammonium magnesium phosphate, one of apatite and calcium carbonate, and one of cystine. Urine culture was positive for growth in all of these patients. Five patients had infection due to B. proteus; 5 with urea splitting Staphylococcus aureus; 3 with P. aeruginosa; 1 with B. coli, and 7 with mixed infections, non-urea splitting. One patient had clinical, laboratory and x-ray evidence of hyperparathyroidism but had refused operative exploration of the neck. Twelve patients in group B required 300 T. R. units daily; 7 required 600 T. R. units daily; 1 required 900 T. R. units daily, 600 in the morning and 300 at night; 1 patient required 900 T. R. units twice daily.

In group B, 2 patients had acceleration of development and growth and passage of stone resulting from sensitization of urinary crystalloids, due to too small amounts of hyaluronidase being administered. One of the failures was a patient with nephrocalcinosis due to renal acidosis. In our experience, hyaluronidase therapy has been relatively ineffective in treatment of 5 of 6 cases of bladder stones. Vesical calculus formation was controlled in a 90 year old man who had previously formed many stones following recumbency as a result of a hip fracture.

An additional 18 patients have received hyaluronidase preoperatively and postoperatively where renal surgery required catheter drainage. In 12 of these, the catheters were maintained free of calcareous deposits. Two paraplegics, not included in these series, should be mentioned. One patient had poliomyelitis and the other was paralyzed following traumatic section of the cord at the level of the sixth thoracic vertebra. Both of these patients had rapidly formed renal calculi soon after becoming recumbent. Hyaluronidase therapy was effective in preventing formation of new stone and growth of existing calculi over a period of 16 months.

There is evidence from preliminary studies that hyaluronidase therapy enhances antibacterial effectiveness of chemotherapeutic and antibiotic agents. This effect is presumably due to dispersing and peptizing action of the increased amounts of protective colloids.

DISCUSSION

Any physician's office or laboratory can make the necessary determinations of the effectiveness of hyaluronidase on clearing of urine. Patients are instructed to self-administer hyaluronidase and control the dosage by observing the urine in the same manner as the diabetic learns to take insulin and test his urine. We arbitrarily attempt to keep the urine clear for 16 to 24 hours following one injection. Occasionally injections must be given twice daily. This is especially so in postoperative or paraplegic patients. The question as to when it is safe to discontinue the therapy cannot be answered at this time. We suspect that patients who tend to form stones readily may have to remain on the regimen indefinitely. Prolonged usage of hyaluronidase therapy has produced no recognizable histopathologic lesions or significant adverse metabolic effects. The long continued application of any program requiring the consistent co-operation of the patient presents certain problems. Some patients tire of daily injections of a drug; and over a period of months, expense to the patient may be a significant factor.

It is most helpful to take the time to be explicit to the patient concerning the nature of his difficulties, to show him his x-rays and to point out to him any change or absence of change in size and number of stones which occurs during the course of therapy. In so doing, the patient becomes more conscientious in following directions and more faithful in closely adhering to the regimen with follow-up care. Finally, he becomes more understanding and co-operative when it appears that stone formation and development is being controlled in his case. The physician's interest and willingness to explain to the patient his problem of renal calculus disease and the objectives of the treatment go far in increasing the possibility of a favorable final result.

SUMMARY AND CONCLUSIONS

Hyaluronidase therapy is an effective adjunctive measure in the control of renal calculus disease. The dosage of hyaluronidase must be determined individually. No severe adverse side effects have been noted when hyaluronidase was properly administered.

The effect of hyaluronidase has been found to be most useful in management of primary, multiple, rapidly recurring, small calyceal stones. Even with the administration of larger doses of hyaluronidase it is less effective in the treatment of secondary calculi. Hyaluronidase therapy is also effective in renal surgery requiring drainage and in renal calculus conditions which present surgical hazards.

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MANAGEMENT OF URETERAL CALCULI

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Certain cases of ureteral calculi are complicated by the presence of one or more factors which dictate choice of treatment and therefore present no therapeutic problem. Among these are patients with stones lodged in the upper or middle third of the ureter, where manipulation is impractical because of their position. If, because of their size, the stones cannot be expected to pass spontaneously, or if they are producing partial or complete obstruction, surgical removal is obviously indicated. Small nonobstructive stones in these areas, on the other hand, may be treated expectantly. It is therefore usually only those stones in the pelvic or intramural portions of the ureter which test the urologist's judgment as to the proper plan of treatment. Calculi obviously too large to pass, those causing considerable dilatation above with renal damage, those associated with severe infection, those producting acute obstruction which cannot be relieved by passage of a ureteral catheter and those in which function of the opposite kidney is also compromised actually present little or no problem, since ureterolithotomy is usually indicated. It is, however, those stones measuring less than ¾ cm. in diameter producing relatively little or no obstruction or renal damage, usually without infection, in which there is a possibility of either spontaneous or manipulative passage, that one must select the plan of treatment which will be least dangerous to the patient and most certain of recovery of the stone, and will entail the shortest hospital stay.

It is, of course, axiomatic that once mechanical intervention is initiated, it must always be followed through until ultimate recovery of the stone, since the effects of instrumental infection, trauma and congestion with resultant obstruction make it practically impossible to terminate any program of mechanical intervention short of recovery of the stone, without the inevitable consequences of renal obstruction, infection, loss of function and perhaps loss of the kidney. With this uppermost in mind, it becomes the obligation of the urologist to decide which of the various methods offers the best chance of recovery of the stone with the shortest morbidity, the least risk and the greatest assurance of preservation of renal function. Among the factors to be considered are the age of the patient, the status of the opposite kidney as well as the one involved, the presence or absence of infection, the size and multiplicity of the stones, the general health of the patient and his financial status. Obviously, operative cystoscopy, when feasible and when it offers a reasonable chance of recovery of the stone, should be the procedure of choice as it entails shorter hospitalization and lower morbidity. Our experience indicates that it is preferable to confine such treatment to use of multiple catheter dilation of the lower segment of the ureter over a period of several days, whenever possible to introduce such catheters, or use of the

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TABLE 1. *Ureteral stone distribution*

SITE	STONES	%
Lower	200	73
Middle	23	8
Upper	51	19
Total	274	100

Johnson wire basket. Occasionally, it has seemed desirable to employ first one and then the other, and in some instances repeated manipulations, provided the patient's general condition as well as the status of the kidney warrant such practice. In other instances, in which the size of the stone, relative loss of function of the involved kidney, presence of severe infection, or status of the opposite kidney suggest that the risks and uncertainties of operative cystoscopy are unjustifiable, we do not hesitate to perform ureterolithotomy immediately, both to protect the patient's renal function as well as to offer the one sure means of removal of the stone. There are always instances, however, in which use of multiple, conservative cystoscopic procedures fails to recover the stone and results in a longer morbidity with ultimate open ureterolithotomy and occasionally some loss of renal function or even loss of the kidney. The ever present possibility of such an outcome has therefore prompted us to compare our results in the management of ureteral stones treated by the various alternative courses.

We have reviewed the records of 274 selected patients with ureteral calculi treated at the Ochsner Clinic during the past ten years. Only those patients whose courses were followed to their ultimate conclusion were included.

Table 1 shows the distribution of the calculi according to site in the ureter. Three per cent of the entire series were bilateral and 9 per cent were multiple.

UPPER URETER

Ninety-four per cent of the 51 stones located in the upper third of the ureter were producing obstruction, 75 per cent of which were more than ¾ cm. in diameter. Twenty-three were associated with infection. Eighty-two per cent of this group were removed surgically and 6 (12 per cent) were subjected to nephrectomy because of complete loss of renal function when first seen. Their average hospital stay was 12 days. Only 3 (6 per cent) were passed spontaneously.

MIDDLE URETER

All 23 stones located in the middle third of the ureter were obstructive and 90 per cent were more than ¾ cm. in diameter. None passed spontaneously. Nineteen (83 per cent) were removed surgically and the remainder (17 per cent) were subjected to primary nephrectomy because of complete loss of renal function when first seen. Their average hospital stay was 11 days.

As can be seen from these statistics, primary ureterolithotomy is usually the procedure of choice in upper or midureteral stones since most of these are large and obstructive. The duration of hospitalization is short and the morbidity is low.

TABLE 2. *Operative cystoscopy*

SIZE	OBSTRUCTIVE		NONOBSTRUCTIVE	
	Cases	%	Cases	%
Under ¾ cm.	49	65	13	17
Over ¾ cm.	10	13	4	5

TABLE 3 *Operative cystoscopy, lower ureter*

	CASES	%	AVER. HOSP. (DAYS)
Successful initial manipulation	34	45	4
Multiple catheters, initial success	14	18	7
Manipulation with extraction by multiple catheters afterward	7	9	9
Spontaneous passage after manipulation	6	8	9
Spontaneous passage after catheters	2	3	8
Ureterolithotomy after manipulation	10	13	25

LOWER URETER

In 81 (41 per cent) of the 200 patients with stones located in the lower third of the ureter the stones passed spontaneously. In none of these was there significant obstruction or renal damage. In only 7 of the 81 stones passed spontaneously was the diameter more than ¾ cm. All these patients were readily accessible to us for continued observation and care, when necessary, so that expectant treatment was possible in this group. In the remaining 59 per cent of cases, because spontaneous passage was considered highly improbable, some form of manipulative or operative intervention was indicated.

Seventy-six (38 per cent) were subjected to operative cystoscopy (table 2). In 82 per cent of these the stones were under ¾ cm. in diameter; 65 per cent were obstructive and 17 per cent nonobstructive. Eighteen per cent were over ¾ cm. in diameter; 13 per cent were obstructive and 5 per cent nonobstructive. Ninety-

TABLE 4. *Lower ureterolithotomy*

TYPE	CASES	%	AVER HOSP (DAYS)
Primary	32	76	15
After op. cystoscopy	10	24	25
Total	42		

TABLE 5. *Nephrectomy*

TYPE	CASES	AVER HOSP. (DAYS)
Primary	10	13
Secondary	2	35
Total	12 (12.5%)	

four per cent of the stones successfully recovered were less than ¾ cm. in diameter.

As can be seen in table 3, thirty-four stones were recovered by initial basket manipulation with an average hospital stay of 4 days, 11 passed immediately after initial multiple catheter dilations with an average hospital stay of 7 days, 7 passed immediately after multiple catheter dilations following failure of basket manipulation with an average hospital stay of 9 days. Eight stones passed later after manipulation or catheter dilation, with an average hospital stay of 9 days. Ten patients were subjected to secondary ureterolithotomy following unsuccessful operative cystoscopy with an average hospital stay of 25 days, in 9 of these the stones were over ¾ cm. in diameter and obstructive. This represented 65 per cent of the stones of this size wherein manipulation had been attempted.

Thirty-two (21 per cent) of the lower ureteral stones were treated by primary ureterolithotomy with an average hospital stay of 15 days and no complications (table 4). Thirty-one of these were over ¾ cm. in diameter, only 6 of which were nonobstructive. Only one of the stones was under ¾ cm. in diameter but it was obstructive. The average hospital stay in this group was 15 days.

Three of the 9 patients with bilateral calculi were treated by bilateral ureterolithotomy. In one patient unilateral ureterolithotomy was done and the opposite side treated expectantly. Primary nephrectomy was performed in 10 patients because of loss of renal function when first seen (table 5).

The complications in general were those of urinary sepsis. This was adequately controlled by free urinary drainage and chemotherapy in most instances. Secondary nephrectomy was required in 2 cases. One resulted from a cortical abscess following operative cystoscopy. Irreparable ureteral damage and infection following manipulation and attempted ureterolithotomy necessitated nephrectomy in the other.

There was one recognized case of ureteral perforation following operative cystoscopy which was drained surgically. The filiform tip of the stone basket disengaged in the ureter in one case necessitating ureterolithotomy and removal of the tip. Injury to the internal iliac vein required ligation of the vessel in one case of lower ureterolithotomy.

In the entire series there were two deaths in the immediate postoperative period, a mortality rate of 0.7 per cent. One resulted from renal failure and the other from generalized tuberculosis.

CONCLUSIONS

✓Stones in the upper and middle thirds of the ureter should be subjected to primary ureterolithotomy unless spontaneous passage seems probable.

Large stones in the lower third of the ureter are best handled by primary ureterolithotomy. Most manipulative failures in this series occurred in patients with stones over ¾ cm. in diameter.

When initial manipulation fails, subsequent manipulations are also unsuccessful in a high percentage of cases and result in a significant increase in morbidity, complications and duration of hospitalization. Ureterolithotomy is, therefore, usually indicated after manipulative failure unless spontaneous passage seems imminent.

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REMOVAL OF URETERAL CALCULUS BY A NEW CATHETER TYPE EXTRACTOR

THOMAS A. DAVIS

Many times I have wished, on passing a catheter by a ureteral calculus, that by some immediate conversion of the catheter, it would become a snaring or grasping instrument. After much thought and experimentation and trial, a device was evolved with which I have removed ureteral calculi, on the first attempt, in four consecutive cases.

The instrument was constructed by passing an S.F. 00 nylon thread through a transverse hole in the ureteral catheter at the 10 cm. mark, and passing each end of the thread into the lumen through separate holes on opposite sides of the catheter at the 15 cm. mark and then down through the lumen until it exits from the outer or butt end. A convenient length of thread is that which will permit about 5 cm. of each end to extend beyond the butt end of the catheter. The nylon thread must be single filament type, because braided is not stiff enough to thread down the lumen. The holes were made by simple needle puncture. A No. 24 hypodermic needle is the right size for making holes for No. 00 nylon S.F. thread (fig. 1). The hole nearest the tip of the catheter must be far enough from the tip so that the tip end of the catheter will not be bent or looped over when traction is exerted on the threads. In making the anchor holes at the tip end of the working segment, the needle may be passed obliquely through the catheter, thus creating a hole in opposite sides of the catheter, but at about 3 mm. different levels from each other. This practically eliminates any weakening of the catheter by the holes.

If the calculus is not too high in the ureter to make it impossible, the segment of catheter above the anchor hole of the thread should be long enough that successive sweeps of the instrument may be made, if necessary, to snare the calculus, without the catheter being withdrawn completely past the calculus. A stylet may be inserted the full length of the catheter lumen with the threads in place. The catheter which I used was of 6 caliber with an olive tip.

Extraction catheters were made by conversion of catheters of other calibers and types of tips with appropriate size of thread and stylets. I use S.F. 00 nylon for No. 6, 000 for No. 5, and 0000 for No. 4 catheters. A stylet slightly smaller in caliber than usually used for a given sized catheter with the end, which is inserted up the catheter, snipped at a rather sharp angle, is more readily inserted in the catheter than the usually furnished stylet with the catheters of a given size. The threads in the catheter do not prevent fluid from being able to pass through it, and it can be used as a catheter to drain the ureter, or to instil lubricant or contrast media into the ureter. Furthermore, sterilizing solution forced in at the butt end will exit at the tip openings, passing the entire length of the lumen. Withdrawal of the threads, exiting from the lumen at the butt end will cause a curving or looping of a segment of the catheter, and with the segment of

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the threads outside of the lumen at that level, will form a complete loop. Withdrawal of the instrument from a ureter with the loop formed above a calculus may serve the purpose of snaring the calculus and removing it, or of dilating the ureter. Once the calculus is well engaged, traction may be temporarily completely released on the threads so as to enable removal of the cystoscope, then reapplied without disengaging the calculus.

The loop can be formed, collapsed, and re-formed within the ureter at any level, at the will of the operator. The size of the loop is controllable within the limits imposed by the distensibility of the ureter, and not dependent upon an uncontrollable balance between elasticity of the instrument and constrictive power of the ureter.

The angulation or looping of the catheter can be done with the stylet in place. A novel feature is, that with a 5 cm. working segment, a 1 cm. withdrawal of the threads will produce a loop of approximately one cm. transverse opening. As with any instrument, good judgment and proper technique are necessary, and the size of the loop formed should be in proper relation to the size of the calculus and the diameter of the ureter. A ureter that will admit an 18F circular bulb, will contain without additional stretching, approximately a 1 cm. width loop of this instrument.

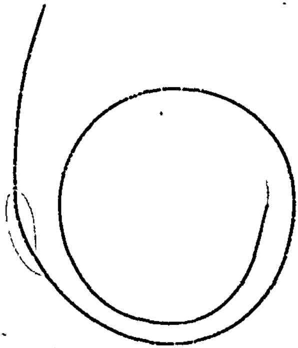

FIG. 1. Photograph of ureteral calculus extractor catheter

✓This calculus extractor can be inserted to any level of the ureter with the simplicity, facility and safety equal to that of an ordinary ureteral catheter of similar size and style. If for some reason, after having snared a calculus in the ureter, it is desired to release the calculus and withdraw the extraction catheter, it may be done following release of traction on the threads, unless, perhaps, there is a complete loop of the catheter part of the instrument around the calculus. By releasing one end of the thread and pulling on the other end, the entire thread may be removed with the catheter in the ureter, thus converting the extractor to an ordinary catheter, except for the remaining thread holes.

✓In the case considered suitable for the use of this instrument, it was cystoscopically inserted up the affected ureter to a distance sufficient to place the loop

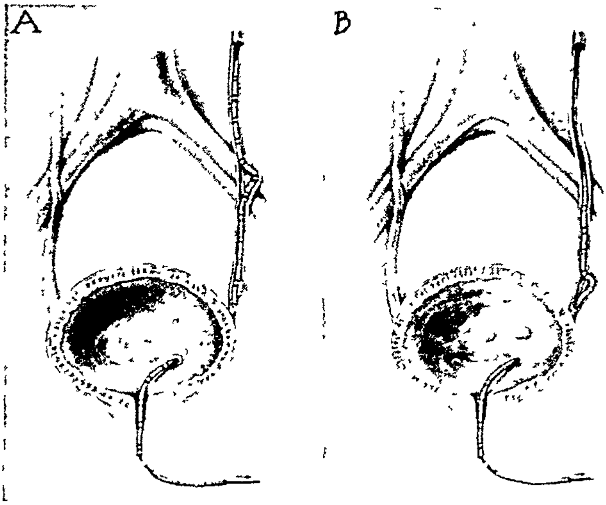

FIG. 2. *A*, loop forming due to traction applied to threads as they emerge from catheter. *B*, stone engaged in loop of catheter.

segment above the calculus, with the stylet in the catheter. The stylet was then withdrawn. The loop was formed (fig. 2, *A*) by withdrawing the threads about 1 to 2 cm. or until a marked resistance to further withdrawal of the threads was encountered. A small hemostat or needle holder with thin rubber covered jaws is convenient for grasping the threads. With the threads in place, either manually, or by clamping adjacent to the butt end of the catheter with a hemostat, and with the other hand manipulating the cystoscope, the catheter was slowly withdrawn with the ureteral orifice under observation. When the loop engaged the calculus, an immediate marked resistance was encountered to further withdrawal of the instrument (fig. 2, *B*). The traction on the threads was then partially released. Combined traction was then made on the threads and catheter to remove the calculus. If the loop should exit from the ureteral orifice without the calculus, it can be collapsed by releasing all tension on the threads and the catheter rotated 90 degrees and re-inserted up the ureter for another attempt to remove the calculus.

The dilatation of the ureter resulting from withdrawl of the formed loop would be advantageous. The instrument can be used as a ureteral dilator when such treatment only is desired. Dilatation of localized segments of the ureter may be done, also. The following 2 cases of which illustrative x-ray films are existant, show the actual use of the instrument.

CASE REPORTS

Case of M. J. Small calculus in lower end of left ureter. Under spinal anesthesia, February 20, 1953, the calculus extractor catheter was passed up the left ureter cystoscopically to the 20 cm. mark. The loop was formed (fig. 3), and the instrument withdrawn. The calculus was engaged and pulled into the bladder, remaining in the loop, and was removed from the bladder with removal of the cystoscope and extractor catheter.

FIG 3

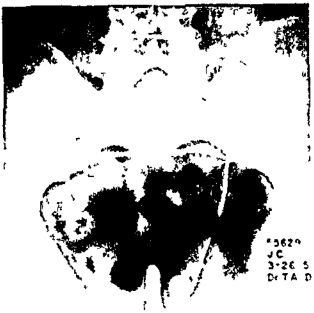

FIG. 4

FIG. 3. Loop formed in ureter

FIG. 4. Extractor has been passed up ureter, loop formed, withdrawn, and calculus engaged. Calculus then removed

Case of J. C. Calculus in lower end of left ureter. Under spinal anesthesia, March 26, 1953, a calculus extractor catheter was passed cystoscopically up the left ureter to the 20 cm. mark. The loop was formed, the catheter withdrawn, the calculus was engaged (fig. 4), and then removed to the bladder. It was removed from the bladder with a McCarthy panendoscope and forceps. The calculus measured 1.2 by .8 by .5 cm.

SUMMARY

A new instrument for the extraction of calculi from or dilatation of the ureter is described.

ADDENDUM

Since the presentation of this paper, stones have been removed from the lower ureter in fourteen consecutive cases, on the first trial, using the stone extractor herewith described.

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URETERAL REGENERATION: EXPERIMENTAL AND CLINICAL

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That the physiology and dynamics of ureteral regeneration is not clearly understood is evidenced by the many types of plastic repair attempted and by the high incidence of failure. The constriction of the ureter from aberrant vessels or hypertrophied musculature, or the very short stricture offers no problem in ureteral regeneration to the surgeon, but our studies are applicable to the longer strictures and to injuries involving the destruction of any considerable portion of the ureter. However, this group is large and we have found that many of the apparently short strictures involve a portion of the ureter at least 1 cm. long. It was the variation in the type of repair of such obstructions by the surgeon and their difference of opinion as to the proper time to continue the internal splint, from five days to five or six weeks, that led us to take the question to the experimental laboratory.

MATERIAL AND METHOD

Sixteen dogs, selected only for their proper size, were operated upon. The anesthesia was pentothal sodium and the skin preparation was tincture of iodine and alcohol. The usual lumbar approach was made, incising the latissimus dorsi and the external and internal oblique muscles. The transversalis fascia and transversalis abdominis muscle were split. The kidney was exposed by incising Gerota's fascia posteriorly. The peritoneum in the dog is tightly adherent to the anterior surface of the kidney and is thin and tears easily. If torn, the defect was sutured immediately. The renal pelvis of the dog is intrarenal, so a point was selected in the ureter from 0.5 cm. to 1 cm. below the kidney, and for a distance of 2 to 3 cm. distal to this point the ureter was completely excised except for a thin strip 2 to 3 mm. in width, but containing all the components of the ureteral wall. This presumably represents an extreme case of ureteral stricture or injury. An 8F red rubber catheter was passed through the middle calyx as a nephrostomy tube and well down into the distal ureter beyond the excised area to act as a splint. Small openings were made in this catheter to allow free drainage of the urine downward, but it was necessary to bury the proximal end under the fascia of the external oblique, for otherwise the dog would tear the tube out within a few days.

The 16 dogs were divided into groups of from two to five animals. In each group a nephro-ureterectomy was done after a lapse of two, three, four, and six weeks following the initial excision of the ureteral segment. The specimens included the kidney and the ureter to well below the injured segment. Sections were made for histological study at four levels; one definitely proximal to the excised segment; two actually through the area of excision; and one definitely below. Thus a comparison was obtained between the normal and the replaced

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area. Paraffin sections were made and stained with hemotoxylin and eosin. Four more dogs were operated upon later in the same manner, especially to check on the condition after four and six week intervals where we believed the maximum regeneration was likely to occur. The sections were made as previously, except that in four animals the section of the ureter were made longitudinally to include the normal ureter both above and below the excised segment. Marking sutures of black silk were placed at the extremities incorporating the splint to keep it from slipping and identify the injured area.

The purpose of the experiment was to observe 1) if a ureteral defect is replaced over a ureteral splint, 2) what time is necessary for such replacement, and 3) what type or types of tissue constitute this regenerated ureteral wall.

RESULTS OF OBSERVATIONS

In this study we were not interested in renal function and did not consider it; our operative technique was designed for the best splinting of the ureter and the observation of any ureteral replacement. We plan subsequent studies of the response of the kidney above the excised area.

The first group of dogs were those re-operated upon after two weeks. In one of these the excised area was marked with the cotton suture, and one dog had a pyelotomy. The hemotoxylin and eosin stains showed normal ureteral components, both proximally and distally, changing quite abruptly in the excised area (fig. 1). Here there was mucosa, although it was thinner than normal and markedly infiltrated with fibrin and inflammatory cells. No evidence of muscularis was present except in a very small segment of the cross section which was undoubtedly the narrow strip of ureteral wall left at the original excision.

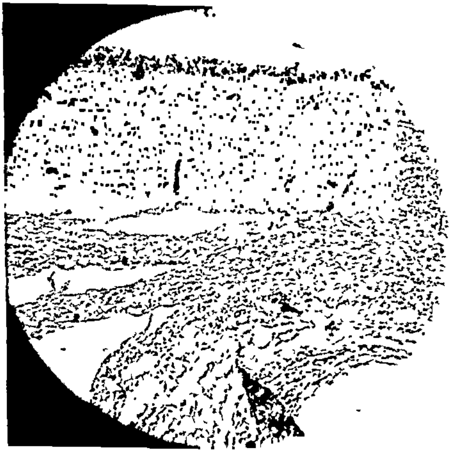

FIG. 1. Ureteral regeneration after 2 weeks

The wall showed marked edema with fibrin and necrotic material, polymorphonuclear leukocytes and lymphocytes.

The second group were re-operated upon at three weeks. Sections were observed in the same manner. Here the mucosa was reformed in the same manner as in the first group of animals, but strands of muscularis could be seen invading

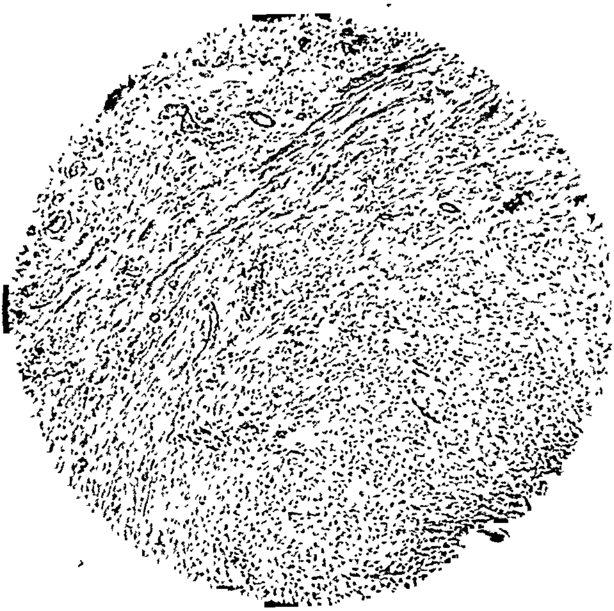

FIG. 2. Three weeks. Muscle strands appearing in regenerating area

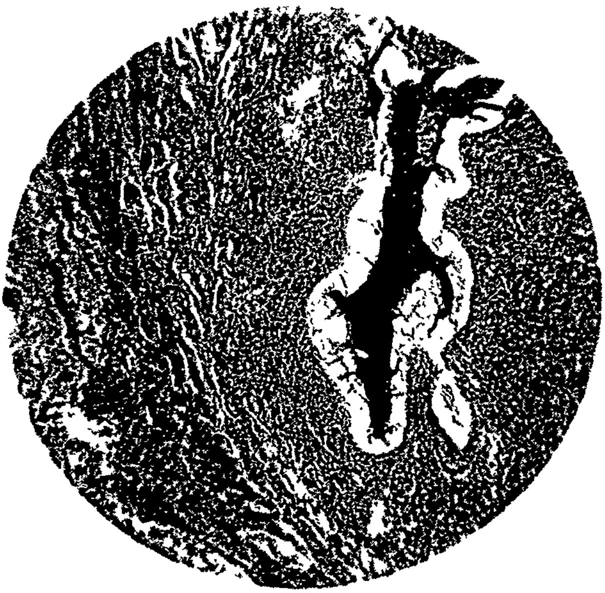

FIG. 3. Muscle strands appearing in inflammatory area after 3 weeks

the inflammatory area (fig. 2), and can be traced around the circumference of the ureter. In one of the specimens there was a patchy area of muscle tissue without confluence around the circumference. The confluent penetration of the muscle was most marked in those with least inflammatory reaction.

Four more dogs were operated upon after an interval of 4 weeks from the original procedure. No great difference was observed between this group and the dogs operated upon after three weeks. The same evidence can be seen of muscle strands invading the area of edema and inflammation (fig 3). The longitudinal section (fig 4) shows the strands of muscle again invading the excised area. Therefore our observation was that though a thin intact mucous membrane replacement is seen after two weeks, little or no evidence of muscularis can be identified at that stage However, muscle tissue is definitely present in varying amounts by the third and fourth weeks.

Since there was little change between the third and fourth week specimens, operation on the next group was deferred until six weeks after the original procedure. Here all components of the ureteral wall are present (fig. 5), although the muscularis shows a configuration different from the normal. The muscle tissue is thinner and does not have the mature thick block-like appearance seen in the normal ureter both above and below the excised area. We cannot yet say whether this is due to its immaturity or to the excessive inflammatory reaction. However, at six weeks all specimens showed permanent canalization of the ureter with mucosa and all muscular components of the wall present. In three of this group we had placed the No. 60 black cotton sutures at the proximal and distal ends of the excised area to identify accurately, both grossly and microscopically, the reformed tissue bridging the surgically made gap in the ureter. All these

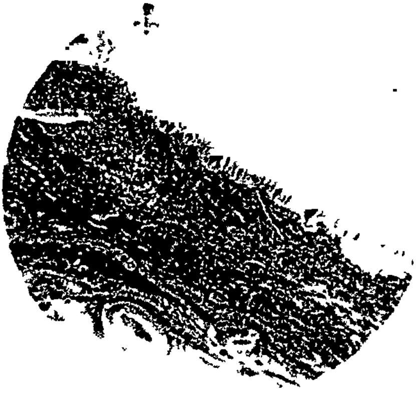

FIG 4 Longitudinal section of ureteral repair after 4 weeks

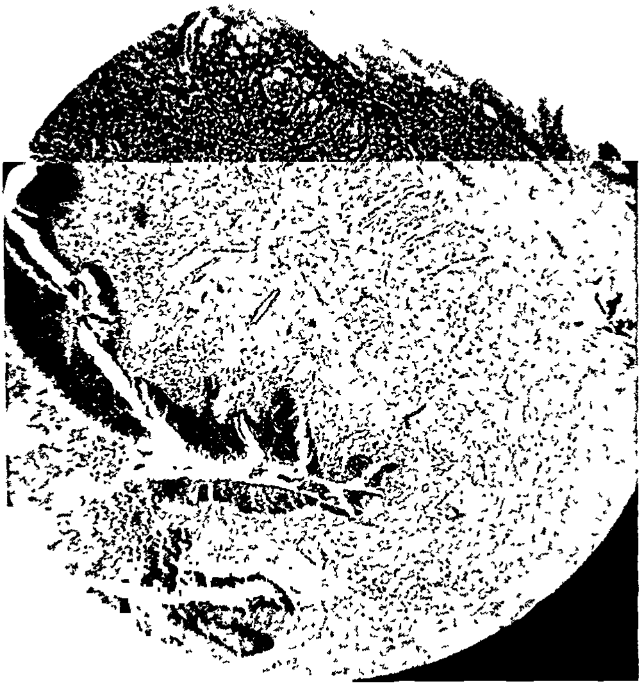

FIG. 5. Almost complete replacement of ureteral wall components after 6 weeks

sutures in the ureteral wall and through the rubber splint were found where they were originally placed six weeks before.

DISCUSSION

The most striking observation in this series was the rapid appearance of smooth muscle in the replaced tissue (three to four weeks), contrary to most of our concepts that smooth muscle does not regenerate to any extent. The whole experiment was plagued by extensive inflammatory and scar tissue reaction, doubtless due to the leakage of urine, since it was technically impossible with these dogs to allow any urine drainage except down the ureteral splint. The kidney, in most cases, appeared to be normal, and the microscopic sections confirmed this opinion.

We had some trouble in deciding whether this is an actual regeneration of ureteral components or only a sliding together of the cut ends. We did observe that the cotton sutures remained as far apart as when they were originally placed. Microscopically, at the 2 weeks' interval the mucosa has already bridged the gap, but there is no muscularis. This is particularly evident in the longitudinal sections. Likewise in the four week sections the muscularis can be seen in the longitudinal sections to be invading an area composed only of inflammatory tissue. Also we noticed that in the six week specimens the muscularis in the previously excised segment is markedly different in appearance than that of the areas both above and below. Moreover the cross sections and the longitudinal sections of the wall in those cases where the ends of the excised areas were approximated show an entirely different picture at the same time interval than those in which the ureteral gap was left open. This may be an academic point, for whatever the mechanism may be, we do see a continuous ureteral wall and a ureter capable of performing normally after an extensive and severe injury. This confirms the findings of David M. Davis in his work on intubated ureterostomy.

In dealing clinically with an injured or diseased ureter one is anxious to answer promptly the following questions:

1) Should the ureter be splinted?
2) Will the ureter reform to function again?
3) How long should the ureteral splint be left in place?
4) How large a defect can be repaired?
5) Will there be a resultant stricture, and can we expect a kidney above it to have sufficient function to support life alone?

These questions have been answered quite satisfactorily as follows:

1) The ureter must of course be splinted.
2) The data suggest that the time required is a minimum of six weeks, after which the splint may be safely withdrawn.
3) The ureter will reform with all its component structures and we know that clinically it will function adequately.
4) From our work we do not know just how large the defect may be that will be closed, but considering the proportionate size of the 50 pound dog and a man we feel that it can be quite extensive.
5) Clinically we have found no resultant strictures. We have felt so confident of our laboratory findings that since 1946, when the project was first begun, we have been splitting long strictures of the ureter over a catheter splint. Several cases are presented here for illustration.

CASE ABSTRACTS

Case 1. A man aged 27 who had moderate hydronephrosis associated with pain had a ureteral stricture 1.5 cm. in length beginning at ureteropelvic junction. The redundant pelvis was excised and the strictured area split throughout its length. A T-tube splint was used and was removed the sixth postoperative week.

Case 2. A 24 year old woman had advanced hydronephrosis associated with persistent pyuria. A stricture 2 cm. long was found at the ureteropelvic junction. The same procedure was followed and the splint removed after six weeks. Ten months later the urine was clear.

Case 3. A boy 4 years of age had bilateral advanced hydronephrosis. The left kidney was nonfunctioning. A 6 cm. stricture of the upper right ureter required almost completely denuding the ureter for 5 cm. T-tube was removed at the seventh postoperative week.

CLINICAL OBSERVATIONS

These patients all had long (1 to 7 cm.) strictures of the uppermost portion of the ureter. Definite diagnosis was made by opening the ureter and finding an inadequate caliber at the narrowed area. However, below the point of stricture the ureter readily admitted the splinting T-tube.

All plastic repair was done with minimal trauma to the cut edges, using plastic forceps and hooks. 00000 chromic catgut on atraumatic needle was used as suture material, as non-absorbable sutures are not suitable in this location. Four surgical principles have been followed meticulously: 1) Obtain dependent drainage of the ureteropelvic junction. 2) Remove all redundant renal pelvis to avoid stasis. 3) Splint the ureter for a sufficient period of time. 4) Keep the wound and the anastomosis dry and free from leakage of urine.

Our results have been uniformly satisfactory with preservation of the function of the kidney. Pyelography does not give an adequate picture of the situation, for a markedly distorted kidney with a large hydronephrosis before surgery does not quite return to our idea of a normal kidney after removing the obstruction. Our criteria of a successful procedure are 1) the patient must be symptom free, 2) the urine must be microscopically clear, 3) the pelvis must empty completely within 15 to 20 minutes after retrograde pyelography, 4) the kidney must have sufficient remaining function to support life, or at least 25 per cent of the total function, and 5) one should be able to pass a 10F or 12F bulb ureteral catheter to the kidney pelvis without obstruction.

The postoperative management of the T-tube consists of attaching its end to a rubber glove, allowing the kidney to drain either through the nephrostomy or the ureter. We have had little febrile reaction and no blocking of the catheter. We have used nephrostomy drainage rather than pyelostomy, as recommended by Davis, as very little renal parenchyma is damaged and we believe that the drainage is better. In a series of 20 cases treated in this way no irrigations have been done and no calcium deposits have occurred to trouble us. The nephrostomy wound closes spontaneously within 24 hours without urinary drainage and the urine should be free of pus by the end of the fourth week after the T-tube is removed.

SUMMARY

Experimentally the ureter shows a marked ability to regenerate all its components.

The mucosa is rapidly replaced, with the muscularis filling in more slowly up until six weeks, when nearly normal components are present.

Clinically we have utilized our experimental knowledge in splinting large defects without reservation, confident of the adequate function of the kidney and ureter involved.

Investigation of the type of peristalsis and of the amount of periureteral fibrosis will be done in future experiments.

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PLASTIC REPAIR OF URETEROSIGMOIDOSTOMIES

HOMER W. HUMISTON

A 45 year old man was initially seen in March 1950, for gross hematuria which had occurred 1 year and 1 week previously. Cystoscopic inspection revealed several square centimeters of the bladder involved with low grade papillary carcinoma. Attempts to deal with the growth transurethrally failed. A transvesical fulguration was done, which was supplemented with additional transurethral fulguration. Six months of these efforts had failed to control the tumor. On September 6, 1950, bilateral ureterosigmoidostomies and a total cystectomy were performed in one stage. The transplants were done by the Coffey 1 technic. Preoperatively, the patient had had no symptoms except hematuria, his blood chemistry was normal, and excretory urography revealed a normal upper tract bilaterally.

For the next 11 months he felt under par, although he worked fairly consistently as a salesman. He would have a degree or more of fever approximately two days out of three. He had several episodes of chills and high fever for which he was hospitalized, a rectal tube placed, and intensive antibiotic therapy prescribed. He consistently described an increasing thirst which he could not satisfy, and failure to regain his strength and endurance. Two months after cystectomy his blood urea nitrogen was 28.9 mg. per cent; 2 months later it was 22.0 mg. per cent; and 4 months later it was 33.6 mg. per cent.

On August 17, 1951, eleven months after cystectomy, the low midline incision was reopened after bowel preparation with aureomycin. No recurrence of the bladder tumor could be demonstrated. A colotomy was done on each side, and the transplants were explored and dealt with through the lumen of the bowel. On the left, no stoma could be found. The dilated ureter was visualized through the bowel mucosa, and was incised for 1 cm. longitudinally. Interrupted sutures of 5-0 chromic were used to bring mucosa to mucosa. There remained a stoma estimated to be 30F. This colotomy was then closed. On the right it was found that the intraluminal stump of the ureter had failed to slough, and was a fibrotic strictured stub about one centimeter long. The ureter above this stub was dilated. The stub was amputated and the ureter was incised about 1 cm. longitudinally, as had been done on the left, and mucosa-to-mucosa sutures were placed. The colotomy was then closed. The postoperative course was entirely uneventful. After a few days the blood urea nitrogen was 12.0 mg. per cent. Since this operation 20 months ago, the patient has felt as well as he did a few years ago, has no abnormal thirst, and has regained his strength and endurance. On April 14, 1953, his blood urea nitrogen was 26.4 mg. per cent, creatinine 1.5 mg. per cent, CO_2 combining power was 36 volumes per cent, and the blood chlorides 714 mg. per cent.

The line drawings traced from the excretory urograms are shown in figures 1 and 2. The hydronephrosis following the anastomoses was more severe on the

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

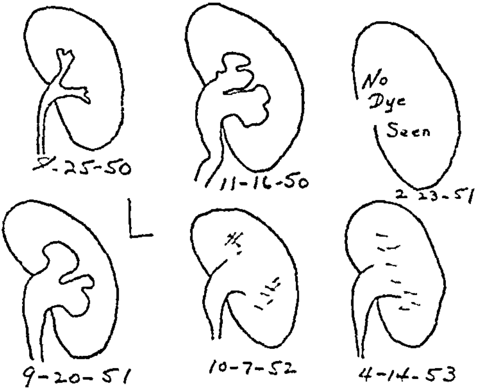

FIG. 1

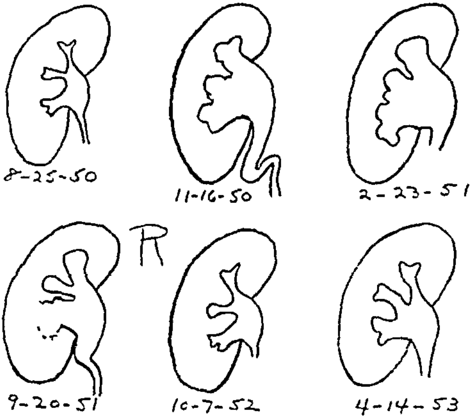

FIG. 2

left, and the improvement following the plastic repair was substantially better on the right

DISCUSSION

Stricture of the terminal ureter occurs not infrequently following ureterosigmoidostomies regardless of the technique used in making the anastomosis It is believed that the incidence of stricture is less when the bowel mucosa is sutured directly to the terminal ureter, but this complication is not thereby eliminated The plastic procedure which was used in this instance is applicable only if the ureterosigmoidostomy has been performed by one of the tunneling techniques

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ELECTROMYOGRAPHY OF THE URINARY BLADDER

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The recording of bio-electric potentials from the musculature of the urinary bladder was initially attempted because of the recognized shortcomings of the conventional cystometrogram.[1, 2, 3] It was also hoped that such electromyographic evaluation might indicate the functional state of the viscus with a degree of sensitivity not heretofore attained.

To this end, transurethral electrodes were so designed (fig. 1) that they might be brought in contact with the lateral walls of the bladder and changes in electro-potentials recorded on a Grass electro-encephalograph suitably filtered. In a series of studies on human subjects[4, 5, 6] it was found that electromyograms so obtained possessed definite and typical characteristics and further that striking and recurring abnormalities in the records were observed in known pathological states.[7] It was, moreover, determined that intravesical pressure changes paralleled the bio-electric shifts. Therefore, electromyography appeared to represent a highly sensitive method for ascertaining the physiological condition of the bladder in diseased states.

Although strong evidence indicated that the records obtained represented true bio-electric potentials arising within the vesical musculature, this evidence was of an indirect nature,[5] and it was therefore deemed desirable to perform experiments of a conclusive character in order to determine whether the electromyograms as obtained *in situ* from the human subject did, in fact, represent potential shifts without artefacts arising solely from the bladder musculature and not from other tissues. It was also thought that laboratory studies might clarify, to a large extent, our fundamental knowledge concerning the origin of the characteristic bio-electric potentials observed.

To this end isolated bladders from a variety of mammalian forms (dogs, cats, rabbits, guinea pigs and rats) were utilized.[8] The animals being sacrificed by means of a blow on the head to eliminate the known effects of anesthesia. These bladders were quickly dissected, including short portions of the ureters and urethra, and were suspended (with fine silver electrodes attached) in a bath of oxygenated Sollmann's solution at 38 degrees centigrade. The electromyograms obtained from such preparations were found, in all respects, to be indistinguishable in contour from those recorded *in situ* from the human subject (fig. 2, *A* and *B*).

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va., May 6-8, 1953.

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myograms are representative of either a) faulty parasympathetic innervation, or b) an atypical response of the diseased musculature to parasympathetic bombardment.

SUMMARY

Electromyograms obtained from the isolated urinary bladders of various mammalian types are indistinguishable in form from records secured *in situ* from normal human subjects.

The frequency of activity as well as the magnitude of bio-electric potentials observed in excised bladder preparations were increased by the administration of parasympathomimetic drugs and by adrenergic blockade. The reverse was found to be true for sympathomimetic substances and parasympathetic blockade.

Records secured from strips of human bladder musculature (fig. 2, *C*) were identical in contour to those obtained from isolated whole bladders, or from the human bladder *in situ*. Maximum activity was shown by tissue samples from the more central portions of the bladder and electropotential activity was minimal in tissue strips from the dome and from the vesical neck.

These findings indicate that the electrocystomyogram secured by way of transurethral electrodes placed within the human bladder represents vesical activity in response to parasympathetic bombardment.

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INTESTINOVESICAL FISTULA: REPORT OF SIX CASES

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Intestinovesical fistula has interested physicians for generations, a description of the condition having been reported in the second century. Harrison Cripps, in his classic monograph, accurately defined and classified this disease entity in 1888. The condition must no longer be considered infrequent as evidenced by the more than 700 case reports since that time. The diagnosis and treatment command the attention of urologists. It is the purpose of this paper to present 6 cases emphasizing the diverse aspects of the disease. We have chosen to use the term "intestinovesical fistula" as advocated by Barnes and Hill. From a semantic viewpoint this is correct as it not only denotes the usual direction of the pathological process, but is also applicable to all portions of the intestinal tract.

CLINICAL FEATURES

During recent years the sex distribution reveals an increasing preponderance of males affected. This is based upon two sound considerations: first, the virtual elimination of pelvic inflammatory disease in the female with the introduction of the modern chemotherapeutic and antibiotic drugs, and, secondly, the barrier to fistula formation offered by the interposition of the uterus and adnexae between the bowel and the urinary bladder. Age distribution favors the middle and older age groups because of their higher incidence of neoplasm and diverticulitis of the colon. It is evident from all studies that a rational classification is based on etiology, namely: 1) traumatic, 2) congenital, 3) neoplastic and 4) inflammatory. Surgery most often accounts for the traumatic fistulas encountered in civilian practice. Congenital fistulas are rare and almost invariably associated with congenital imperforate anus. Neoplastic fistulas result from a multitude of primary lesions arising in the genito-urinary and lower intestinal tracts. Inflammatory fistulas also result from numerous causes, but of paramount importance and interest is diverticulitis of the colon. Diverticulitis is truly a widespread disease. This is apparent from the finding that 5 to 8 per cent of patients with symptoms sufficient to warrant roentgenological examination, demonstrate evidence of diverticulosis. Approximately 20 per cent of those with diverticulosis have associated diverticulitis.

SYMPTOMS AND DIAGNOSIS

The pathognomonic symptoms of intestinovesical fistula are referable to the urinary tract. Pneumaturia and the passage of feces per urethram, when associated with dysuria, urgency, frequency, hematuria and suprapubic pain, leave little doubt as to the diagnosis. The remainder of the clinical picture will be determined by the exact nature of the underlying etiology. Urinalysis will generally

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reveal various degrees of pyuria, bacilluria, hematuria and fecaluria. Cystoscopy has been shown to be the most informative diagnostic procedure. However, actual visualization of the fistulous opening is not always possible. Often one merely gains presumptive evidence in the form of a localized area of cystitis and edema. The cystogram may provide an exact diagnosis by revealing an extravesical extension of the contrast medium into the bowel. Barium enema aids in the diagnosis of the underlying bowel disease but is much less efficacious in depicting the actual fistula. Sigmoidoscopy is even less informative in this regard. The use of various dyes to demonstrate a communication between the intestinal tract and the bladder has been of value in some cases. In spite of all these diagnostic adjuncts, however, the actual demonstration of the fistula many times must await surgical exploration. It should be emphasized that, given the pathognomonic symptoms, a diagnosis of intestinovesical fistula must be maintained even though objective substantiation is lacking.

Recognition of an "incipient fistula" is equally important. The appearance of dysuria, urgency, frequency and tenesmus in a patient with intestinal disease precedes the development of the fistula in many cases. Adequate treatment during this phase of the disease may prevent the subsequent fistula formation.

CASE REPORTS

Case 1. J. O., No. 22652, a 59 year old white man, was admitted to the Long Beach Veterans Administration Hospital on October 29, 1951, in a semi-comatose condition with symptoms of an intractable cystitis of 2 months' duration. A past

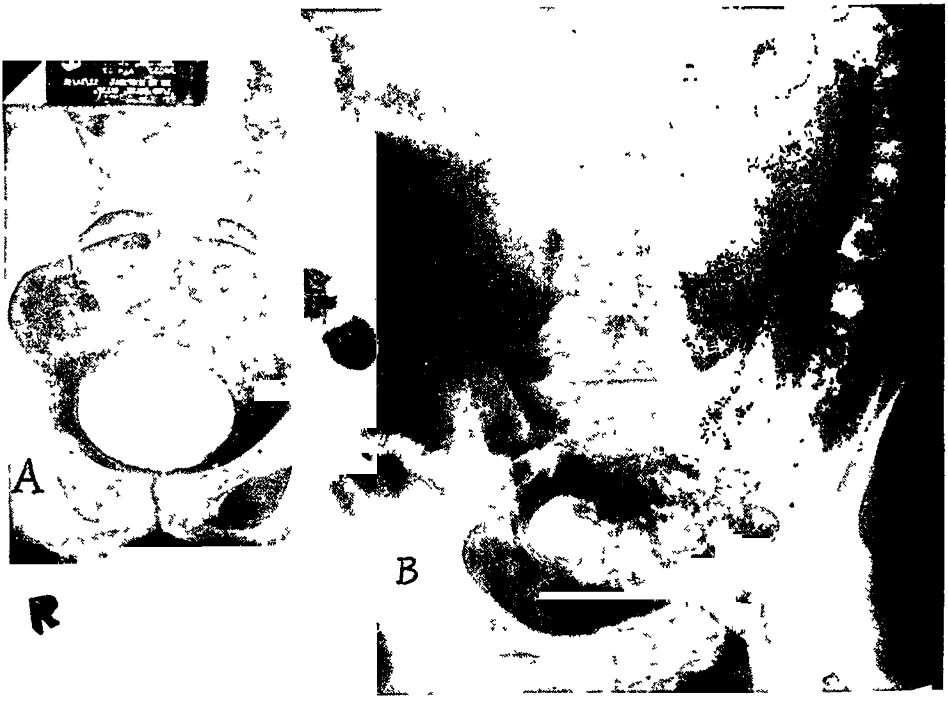

FIG. 1. *A*, cystogram fails to reveal fistula. *B*, barium enema discloses diverticulosis of colon.

history of "nephritis" and pulmonary tuberculosis was elicited. Physical examination revealed a chronically ill, dehydrated patient with moderate tenderness in the left costovertebral angle. The prostate was slightly enlarged, very soft and tender.

Initial laboratory studies revealed blood urea nitrogen of 127 mg. per cent and a CO_2 combining power of 7 meq/L. Urinalysis revealed numerous leukocytes, 10–12 red blood cells and many coarse granular casts. Urine culture revealed a moderate growth of A. aerogenes.

Cystoscopy on November 4, 1951, revealed an area of cystitis and edema surrounding the left ureteral orifice. A small amount of fecal material was present but a definite fistulous opening could not be identified. Cystogram disclosed an irregular outline suggesting cellule formation but no fistula was demonstrated (fig. 1, *A*). Proctoscopy following intravesical instillation of methylene blue failed to demonstrate the fistula. Barium enema disclosed diverticulosis of the colon (fig. 1, *B*). An organic carmine dye, which is not absorbed from the intestine, appeared in the urine four hours after oral ingestion. Careful anamnesis at this time brought out a definite history of pneumaturia and passage of feces per urethram.

On January 2, 1952, surgery revealed extensive diverticulosis of the colon with an area of diverticulitis extending downward from a point 6 cm. above the peritoneal reflection. The involved segment measured 10 cm. in length and a definite fistulous tract was found to communicate with the left posterior vertex of the bladder. The fistula was divided, the bladder closed and an anterior resection without diversional colostomy was performed.

The postoperative course consisted of chronic pyelonephritis with increasing renal insufficiency, chronic acidosis and nephrolithiasis. At no time was there any further difficulty from the sigmoidal-vesical fistula. Cystoscopy and cystogram 14 months later revealed no evidence of fistula.

Case 2. H. S. M., No. 14419, a 43 year old white man with post-traumatic hemiplegia and aphasia, experienced sudden severe lower abdominal pain during defecation. Urinary tenesmus was followed by acute retention. Catheterization

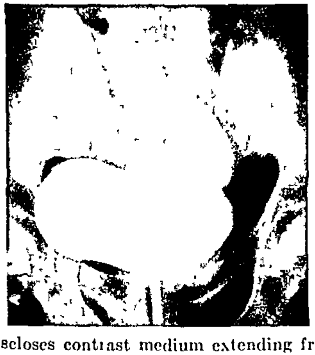

FIG. 2. Cystogram discloses contrast medium extending from bladder into colon

revealed grossly bloody urine. On October 24, 1950, the fifth day of illness, the patient was transferred to the Long Beach Veterans Administration Hospital.

Physical examination revealed an extremely dehydrated, acutely ill patient. The abdomen was distended and tympanitic. Diffuse tenderness with spasm and rebound tenderness in the LLQ was present. Bowel sounds were absent.

Cystogram disclosed a definite vesicocolic fistula (fig. 2). Cystoscopy revealed a 5 mm. opening, with necrotic grayish-white margins, in the left posterior aspect of the vertex. On October 25, 1950, a transverse colostomy was done and a generalized peritonitis due to E. coli was found.

Six months later the cystogram of the asymptomatic patient revealed a smooth contour and no evidence of the previously demonstrated fistula. Barium enema and sigmoidoscopy were normal. On May 23, 1951, laparotomy revealed only old inflammatory adhesions between the recto-sigmoid and bladder and the colostomy was closed.

Case 3. K A. S., No. 33157, a 35 year old white man, was admitted to the Long Beach Veterans Administration Hospital on July 9, 1952, complaining of urinary frequency, urgency, dysuria, terminal pneumaturia and passage of food particles per urethram. A subtotal colectomy with permanent ileostomy had been performed 9 months previously following unsuccessful medical management of chronic ulcerative colitis (fig. 3, *B*).

The patient was poorly nourished and chronically ill. He had a healed surgical scar with an ileostomy in the right lower quadrant. A small amount of purulent drainage was present at the site of the previous colostomy.

Repeated urinalyses revealed 1 plus albumin, numerous leukocytes, 10–15 red

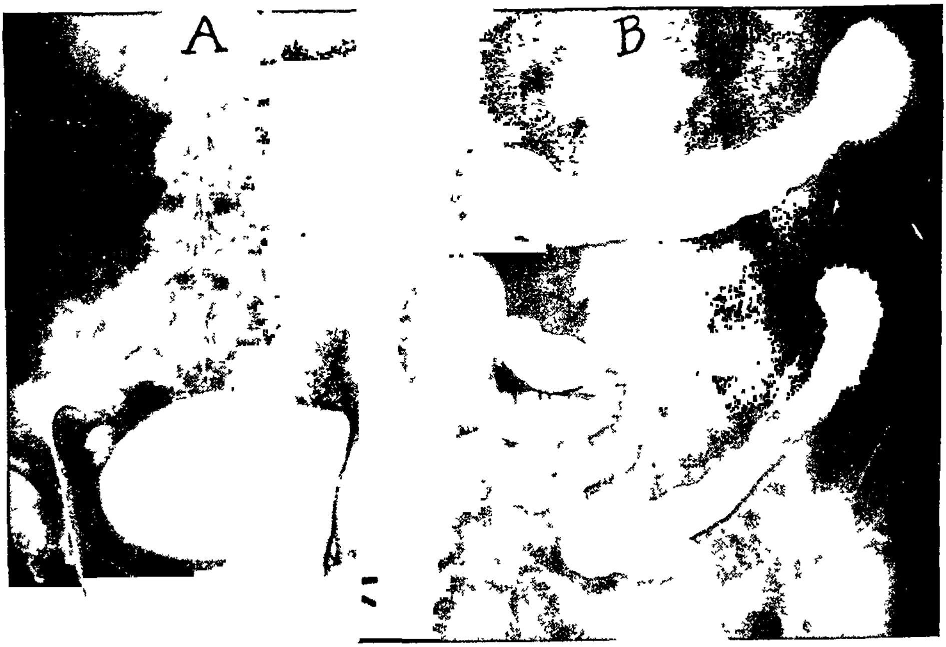

FIG. 3 *A*, cystogram fails to disclose fistula. *B*, barium enema discloses typical appearance of chronic ulcerative colitis

blood cells and numerous motile bacteria. Cystogram, including films delayed by 30 and 60 minutes, failed to demonstrate extravesical extension of contrast medium (fig 3, *A*). Cystoscopy showed a small, circumscribed area of bullous edema 4 cm. posterior and lateral to the right ureteral orifice. A toothpaste-like material was seen to extrude from the lower margin of this area. Below this point a small diverticulum of the bladder wall was noted.

Surgery on July 28, 1952 disclosed dense inflammation about the distal loops of ileum with a well organized abscess cavity adherent to the bladder. A fistulous tract led into the abscess cavity and originated 10 cm. proximal to the ileostomy. Two additional small ileo-ileal fistulae were identified. The terminal 30 cm. of ileum were resected and the opening in the bladder was closed. The patient was free from urinary symptoms nine months later.

Case 4. C. P., No. 35211, a 51 year old white man, entered the Long Beach Veterans Administration Hospital with severe pain in the left lower quadrant and tenderness radiating to the suprapubic region. Similar episodes had occurred 5 times in the past 6 years. Ten months prior to admission, pneumaturia and dysuria developed

Physical examination revealed an acutely ill patient with marked tenderness in the left lower quadrant and suprapubic region. Barium enema revealed diverticulitis of the colon (fig 4, *B*).

On August 22, 1950, a transverse colostomy was performed, followed by daily irrigations of the distal loop with sulfathaladine solution. Two weeks later cystoscopy and cystogram (fig. 4, *A*) failed to reveal evidence of intestinovesical fistula, but bilateral vesico-ureteral reflux was noted. Methylene blue instilled into the bladder was recovered from the distal loop. The patient failed to return for definitive surgery until 27 months later. During this interval he had been working and was free of symptoms except for two episodes of cystitis

Surgery on October 7, 1952, demonstrated diverticulosis with a definite di-

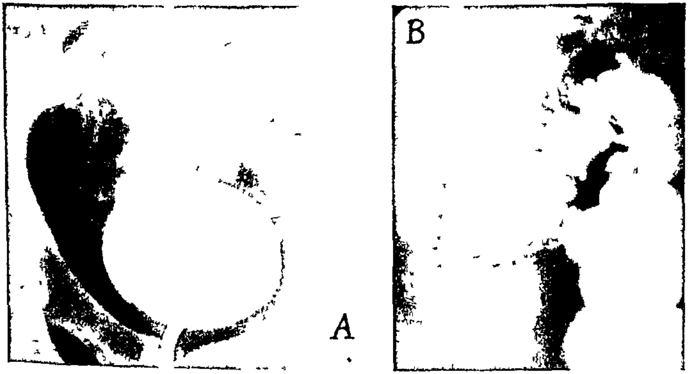

FIG 4 *A*, cystogram fails to disclose fistula, but bilateral vesico-ureteral reflux is apparent *B*, barium enema demonstrates diverticulitis

verticulitis involving the sigmoid 6 cm. above the peritoneal reflection. The sigmoidal-vesical fistula was divided and an anterior resection performed. The colostomy was closed 22 days later. Although peritonitis and wound evisceration complicated the postoperative period, the patient was ultimately discharged without further urinary symptoms.

Case 5. H. P. W., No. 38646, a 71 year old white man, was admitted to the Long Beach Veterans Administration Hospital on December 13, 1951, complaining of rectal bleeding, abdominal pain and a change in bowel habits. Rectal examination showed induration at the base of the bladder on the left but no mass was palpable.

On urinalysis 10–15 leukocytes and a rare red blood cell were found. Stools were positive for occult blood. Repeated barium enemas were unsatisfactory because of complete obstruction at the rectosigmoidal junction (fig. 5, *B*). Urologic consultation elicited a history of increasing cystitis with pneumaturia and passage of feces per urethram. Cystocopy revealed an intense diffuse cystitis with marked spasm and reduction of capacity. A 2 cm. opening on the left lateral wall of the bladder was seen and proved to be an intestinovesical fistula on cystogram (fig. 5, *A*).

On June 11, 1952, a preliminary transverse colostomy was performed following which the urinary symptoms subsided. Definitive surgery on August 11, 1952 disclosed a large ulcerated carcinoma of the sigmoid, 10 cm. above the peritoneal reflection, which invaded the bladder. An anterior resection of the lesion was done, the opening in the bladder closed, and a suprapubic cystostomy performed.

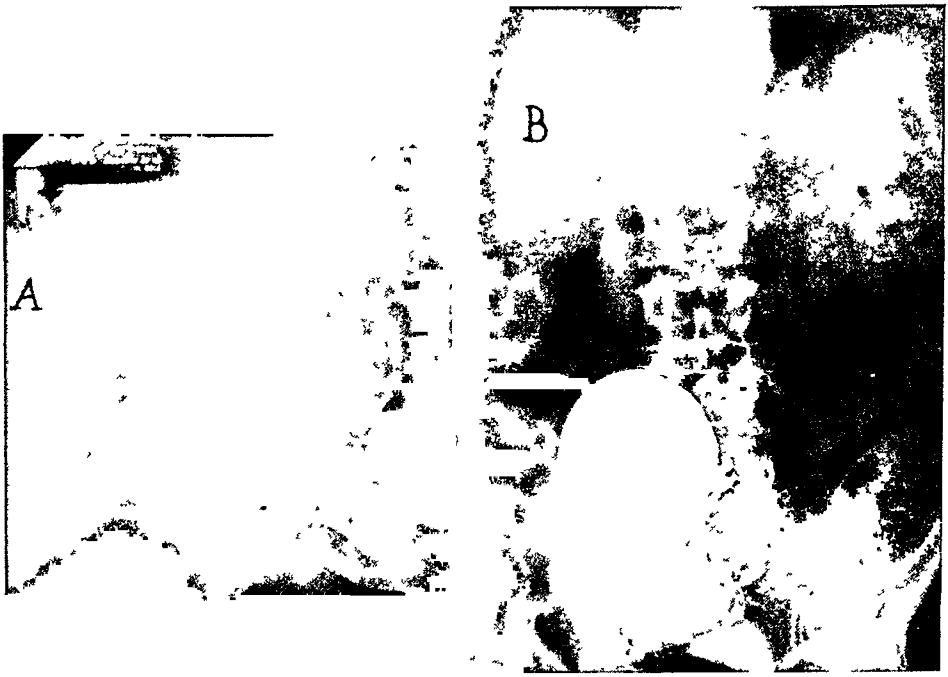

FIG 5 *A*, cystogram demonstrating extension of contrast medium from bladder into colon *B*, barium enema reveals complete obstruction at rectosigmoid.

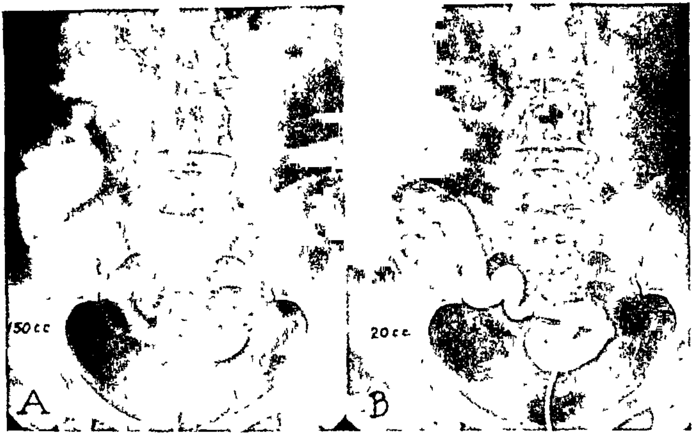

FIG 6. Injection of contrast medium into fistulous opening in bladder outlines ileum and reflux into colon with increased volume of medium (Courtesy of Dr. S K Bacon.)

Two months after discharge the patient returned with a recurrent suprapubic urinary fistula. The urine was heavily infected. Cystostomy drainage was re-established. On February 9, 1953, acute pulmonary edema developed and failed to respond to cardiac treatment; death occurred 2 days later. Necropsy revealed residual carcinoma in the colon, a huge cauliflower mass of tumor extending into the bladder and distant metastases in the liver.

Case 6. F. W. M., No. 42386, a 40 year old white woman, entered the Long Beach Veterans Administration Hospital with a history of pneumaturia and passage of feces per urethram following peritoneoscopy for lysis of adhesions A history of nine previous surgical procedures was elicited.

A fistulous opening was seen on cystoscopy prior to admission. Catheterization of this opening with injection of contrast media clearly defined an ileovesical fistula (fig. 6). Neither small bowel studies nor barium enema demonstrated this fistula.

On March 25, 1953 the ileovesical fistula was divided, the bladder closed and the involved segment of terminal ileum resected.

DISCUSSION

Our experience with 6 cases of intestinovesical fistula is in accord with previous studies. Pneumaturia and fecaluria were diagnostic and present in all cases except case 2 which was of an emergency nature with an unreliable history. This patient is similar to one reported by Harlin and Hamm in whom inability to void was the primary urologic symptom associated with an acute perforated diverticulitis.

Cystoscopy was the most reliable diagnostic procedure. The fistulous opening was actually visualized in 4 cases. The clue to diagnosis was the finding of feces

TABLE 1.—*Relative merit of various findings in establishing a diagnosis of intestinovesical fistula*

CASE	CYSTOSCOPY	BARIUM ENEMA	CYSTOGRAM	DYES	PROCTOSCOPY	PNEUMATURIA	DIAGNOSIS & TREATMENT
J. O. No. 22652	Positive (Feces in bladder plus localized area of cystitis)	Negative	Negative	Positive	Negative	Positive	Diverticulitis One stage resection Cure
H. S. M. No. 14419	Positive (Fistula visualized)	Not done	Positive	Not done	Not done	?	Acute perforation diverticula Colostomy alone Cure
K. A. S. No. 33157	Positive (Fistula visualized)	Not done	Negative	Not done	Not done	Positive	Ulcerative colitis Resection & ileostomy Cure
C. P. No. 35214	Negative (Not done until two weeks after colostomy)	Negative	Negative	Positive	Not done	Positive	Diverticulitis 3 Stage resection Good 3 mos. post-op.
H. P. W. No. 38646	Positive (Fistula visualized)	Negative	Positive	Not done	Negative	Positive	Carcinoma 3 Stage resection Death
F. W. M. No. 42386	Positive (Fistula visualized)	Negative	Positive	Not done	Negative	Positive	Traumatic One stage resection

in the bladder in an additional case. The one instance of a negative cystoscopic finding concerns the case in which cystoscopy was delayed until 2 weeks after diversion of the fecal stream. While barium enema failed to demonstrate the fistula in any of the cases, it was very helpful for the diagnosis of the underlying bowel disease. The use of dyes was helpful in two cases. The contribution of proctoscopy and sigmoidoscopy proved to be of no value. These data are summarized in table 1.

Recognition of the underlying disease responsible for the intestinovesical fistula is the prime consideration in surgical management. In general, a multiple stage procedure with preliminary colostomy is the treatment of choice. In carefully selected cases with minimal inflammatory involvement, a one-stage resection without colostomy offers good results with less morbidity. A cure by colostomy alone was obtained in one case, and in all cases symptoms were relieved by colostomy. Our case with carcinoma of the colon confirms the experience of others, namely, that palliation is usually all that can be accomplished. The prognosis in carcinoma of the colon has been shown to be considerably poorer when involvement of the bladder is present. With an actual intestinovesical fistula lined by carcinoma cells, the prognosis is almost uniformly fatal.

SUMMARY

The clinical features of intestinovesical fistula are reviewed.

Six cases, illustrating various primary etiologic diseases, are presented.

The importance of pneumaturia and fecaluria is emphasized. Cystoscopy is the most informative diagnostic procedure.

Treatment, in most cases, consists of multiple stage surgery with preliminary colostomy. However, in selected cases, a one stage resection is advocated.

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UTEROVESICAL FISTULA WITH FETAL PARTS PRESENTING IN EXTERNAL URETHRAL MEATUS

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It was of interest to learn, in review of the literature, that before this same organization and in the same state of Virginia, MacKenzie in 1921 presented a paper on the same subject of uterovesical fistula. Presenting circumstances however were considerably different. As late as 1950 Stening stated, "this type of fistula is so rare that it does not find a place in most manuals of obstetrics and gynecology." We were not in complete agreement with this statement because several case reports were encountered. A rather diligent probe of all publications back to 1876 on the subject of uterovesical fistula fails to reveal a single instance where fetal parts were demonstrable within the bladder and presenting through the urethra as a complication of the pregnancy.

The girl's history was quite informative. A 30 year old white female gravida 4, para 0, presented herself to her family physician August 20, 1951 approximately 6½ months pregnant for prenatal care. Her past history revealed that her first pregnancy was 11 years prior to this time. Her labor was difficult and her child died as a result of toxemia of pregnancy. Her old hospital record said that she leaked urine from her vagina following delivery and returned in 3 months for vaginal repair of a vesicovaginal fistula. Apparently the uterovesical fistula was unrecognized. Since that time, 11 years ago, menses had stopped but cyclic voiding of blood in the urine occurred every month and has persisted to date. She did not need to wear a pad and it was not necessary to interrupt intercourse. Three years later a cesarean section was done for a 6 months dead fetus. She stated that 5 years later she miscarried a 3 months pregnancy through her bladder.

The examination at this time (August 20, 1951) by her family physician showed everything to be essentially within normal limits except that fetal heart tones could not be heard. Blood Kahn was negative. One week later she was admitted to the Methodist Hospital because of lower abdominal cramping interpreted to be uterine contractions. A vaginal examination demonstrated a long, thick cervix with no dilatation. No fetal heart tones could be heard. A torn fetal scalp could be seen coming from the urethra. At this stage we were called to see the patient for the first time (fig. 1). Cystoscopic examination revealed loose pieces of the scalp of the dead fetus with broken pieces of head bones. Visualization at this time was considerably impaired due to the space-occupying foreign body in the bladder. General surgical consultation advised open section which was done immediately. The uterus was closed, a tubal ligation performed but no attempt made to repair the fistula at this time. This was the judgment of the surgeon as he felt the patient's general condition precluded further surgery. Her postoperative course was uneventful and all lochia was discharged through the bladder. An excretory urogram prior to her dismissal on the seventh post-

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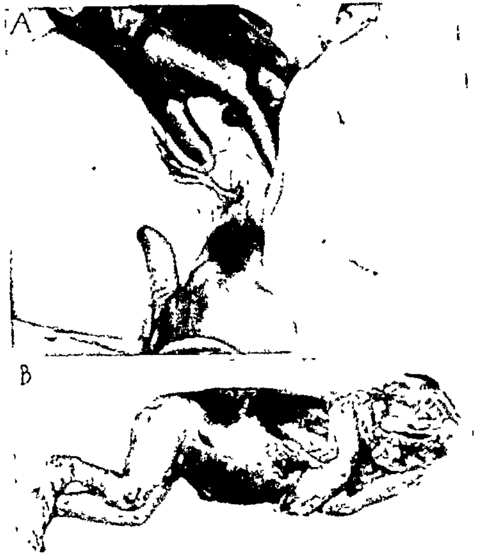

Fig. 1. *A*, fetal scalp emerging from urethra. *B*, dead fetus as it appeared following cesarean section. Note absence of scalp and broken head bones.

operative day showed a normal upper urinary tract. Arrangements were made for her to be re-admitted to the hospital in approximately 3 months' time for repair of her fistula.

Approximately a year later the patient entered the hospital again. Cystoscopic examination showed normal bladder with a fistula opening on the posterior wall in the midline. Repeated cystograms failed to demonstrate communication with the uterus. Upper tract studies were again normal. Urinalysis was negative. On October 1, 1952, through a midline incision, the bladder was opened, the fistulous tract excised and the uterus removed leaving the cervix. The bladder was closed and drained with a urethral catheter. The patient's postoperative course was again without complication and the urethral catheter was removed on the tenth day. She was discharged on the fourteenth day. Follow-up cystoscopy was done one month later and a normal bladder found. There was no urinary difficulty.

COMMENT

From the published data nearly all uterovesical fistulas were secondary to obstetrical procedures or sequelae of radium application, surgical accidents, carcinoma and occasionally tuberculosis. The uterine opening is rarely found in the corpus uteri but nearly all were located in the cervical canal which gave the patient vaginal leakage of urine. There was no vaginal leakage of urine present in our case, therefore placing the opening above the internal os. The conclusions reached by Sims in 1928 summarize well this subject. I see no reason today to vary his remarks which are as follows:

1) Uterovesical fistulas may be due to trauma in labor with the use of forceps, either by carelessness or incompetence especially in attempt at rotation.

2) They may be caused by uninterrupted prolonged labor with the head on the pubic rami and bladder with strong uterine contractions.

3) According to the histories of the reported cases the complication was not caused by the accoucheur, though he may be reluctant to report in the majority of instances.

4) Practically all fistulas occurred in cases of prolonged labor, contracted pelvis, or a combination of the two, with the bag of water rupturing several hours previous to delivery.

5) The use of pituitary extract may play a part.

6) The incidence is probably more frequent than is observed or reported.

CONCLUSIONS

A case has just been described of a 30 year old white woman 6½ months pregnant, presenting fetal parts in the urinary bladder and through the external urethral meatus.

Several instances of uterovesical fistula have been reported, as evidenced in the bibliography, but to our knowledge ours is the first with this added feature.

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THE TREATMENT OF PRIMARY CARCINOMA OF THE BLADDER

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We have consistently leaned toward conservative treatment of bladder cancer because the results reported from cystectomy and ureterosigmoidostomy have not been sufficiently impressive to convince us that equally good or better results may not be obtained from less radical methods. Recent contributions by Creevy,[1] Kligerman et al.,[2] Colby and Kerr[3] and others serve to sustain this opinion. Reports dealing with the late results of uretero-intestinal anastomosis have now appeared in sufficient numbers to emphasize the prevalence of subsequent renal failure even in the few cases in which the cancer has appeared to have been controlled. (A repetition of quotations designed for argument from either viewpoint of this important subject will serve no pertinent purpose.)

The degree of malignancy and the extent of growth in a tumor are primary factors upon which intelligent treatment will be based. The determination of these factors with a fair element of accuracy is difficult. In the case of bladder tumors, the location of the lesion within the organ must also be considered, along with the age and general condition of the patient. Fortunately in this day of advanced surgical techniques, antibiotics and ancillary services, primary surgical mortality is much less to be feared than was formerly the case. This may at times lead one to use radical methods without due regard for late morbidity or mortality. Conversely, cancer is a deadly disease and every reasonable effort should be made to entirely remove or destroy the tumor. Each case is to be considered an individual problem with the surgeon assuming the role of the good doctor in his efforts to do all that the case requires commensurate with safety and the ultimate welfare of the patient.

In considering the degree of malignancy of a given bladder tumor, the appearance at cystoscopy will usually differentiate those of the two extremes. The pedunculated papilloma with a long pedicle is practically always benign and while it may recur from transplantation it is not invasive and is not to be considered malignant. The sessile type and those papillomas with short broad bases must be regarded as likely malignant. A biopsy taken from the base of any of these growths and submitted to pathological study will permit a more accurate evaluation of the degree of malignancy as shown primarily by the tendency of the tumor cells to invade the bladder wall. The majority of cases will fall in the latter category.

This fact tends to stress the importance of the pathological report. Jewett,[4] Marshall[5] and others have emphasized the importance of the degree of penetration as related to treatment and prognosis. This must be kept in mind in securing

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Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26–29, 1953.

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[2] Kligerman, M. M., Robinson, J. N., Fish, G. W. and David, I.: J. Urol., **68:** 706, 1952.

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the biopsy specimen. The resectoscope loop employing a very high frequency current is our best available instrument for this purpose. However, it is far from ideal. In dealing with the flat invasive tumors a fair specimen of tissue may be secured without danger of perforating the bladder wall. The more papillomatous growths with broad bases that are not easily visualized offer more difficulty. Puncture of the bladder with extravasation can easily occur. This is mentioned because of the constant plea for larger and deeper biopsy specimens. If the specimen has been adequate in depth and special attention directed toward it by the pathologist the extent of invasion into the bladder wall at that particular point may be determined Few such specimens are secured and even when they are, too much emphasis must not be placed on the pathological report in the overall estimation of the real degree of invasion and extent of the tumor. Cancer seldom grows symmetrically and penetration may be much deeper at some point outside the biopsy area In fact many of these invasive tumors grow in the plane of the bladder and may extend deep laterally for some distance beyond the bounds of the lesion presenting in the bladder. Graves[6] has expressed our view in this regard: "The adequate preoperative biopsy is not so simple as it sounds and perhaps not so important " One must conclude that the biopsy report is simply one factor to be considered in the final analysis; other findings may be more conclusive

Bimanual rectal or vaginal examination under anesthesia perhaps gives the best index, in most cases, to the extent of invasion of these tumors. If a mass is present in the area around the tumor, its size and degree of mobility will convey to the trained examiner a definite impression of the extent of growth

From the cystoscopic examination, the biopsy report and bimanual examination, one usually can determine with fair degree of accuracy the type of tumor and its degree of penetration. The location of the lesion within the bladder must be considered, whether it is located at the base or above, and whether either ureteral orifice or the urethra is involved or threatened with invasion Evaluation of all these factors is necessary in determining the type of treatment to be applied. Each case must be considered on its individual findings Flocks[7] has stressed this point and urged that the surgeon not attempt to classify cases too sharply into groups and apply treatment as related to the group but rather to fit the therapy to the particular case In the treatment of bladder cancer (the two extreme degrees of malignancy excluded) one must realize that he is to proceed with a considerable degree of doubt as to the actual potentialities and extent of the disease Conjecture or inference gained from one or more elements of the examination may lead to over-emphasis of one and lack of regard for the other.

In the discussion of treatment we would consider bladder tumors in only two broad classes, the benign papilloma and the invasive tumors, whether they be papillomatous or sessile. All seem agreed that the former are to be treated by simple fulguration This is usually done cystoscopically or in some cases of multiple lesions, suprapubically. When multiple, with a tendency to recur in various locations (papillomatosis), x-ray therapy is often used

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[6] Graves, R C Discussion of Jewett's paper, J Urol , 67: 677, 1952
[7] Flocks, R H J A M A , 145: 295, 1951

In the treatment of invading carcinoma, whether superficial or advanced, we have relied upon the combination of surgical removal when possible, supplemented by radiation, usually with radon seeds. There is ample evidence that most bladder tumors are radiosensitive. As late as October 1952, Kligerman et al.[2] reported a group of 347 cases, 198 of which were treated by radium alone and 149 by segmental resection. Their conclusion was "A higher percentage of patients with carcinoma of the bladder are clinically free of the disease at any given time following radium implantation than a similar group treated by segmental resection." In support of the ineffectiveness of surgery alone in penetrating tumors, Jewett[8] reports that there were only 3 per cent survivals after 5 years following complete extirpation of the bladder in tumors that had invaded deeply into the bladder wall. This is small hope to hold out to patients upon whom so major a procedure is to be carried out, it being remembered that there is no accurate way to determine exactly preoperatively the extent of invasion. Colby and Kerr[3] state that total cystectomy in their hands gave only 10 per cent 5-year cures if the bladder muscle had been invaded to any extent. The extremely radical cystectomy reported by Victor Marshall[5] has yet to be evaluated. He states that 104 such operations were done in which the entire contents of the pelvis were removed except that in 51 the rectum was left in place. No mortality nor morbidity facts are mentioned. We have seen no patients in whom we have felt that such a procedure was justifiable.

In a series of 95 consecutive cases we found 30 to be simple, noninvasive papilloma. All of these 30 cases were treated by fulguration through the cystoscope except for 3 treated by suprapubic fulguration because of the multiplicity of the growths and their location. None of the patients has died as a result of his bladder tumor.

The remaining 65 showed some evidence of invasion either by pre- or postoperative biopsy study. Twenty-three were found suitable for only palliative treatment. Included are cases in which an exploratory operation was done and too extensive invasion found to warrant attempts to remove the tumor. Also are included a number of senile patients in whom no form of treatment could be carried out.

The remaining 42 cases compose those of invasive carcinoma of all degrees, from the most superficial to those in which the tumor extended deeply into the muscle. These patients were operated upon by several methods: 1) deep fulguration cystoscopically with radon implantation; 2) suprapubic fulguration with radon implantation (largely tumors of the bladder base); 3) segmental resection after fulguration, and radon implantation. In 4 of these in which the ureteral orifice was involved, the ureter was transplanted into another location in the bladder.

There were no primary surgical deaths in this series of 42 patients. Postoperative x-ray treatment was carried out at some period after the operation in the majority of the cases. All the treatment by radiation both by radon and x-ray was done in cooperation with a radiologist.

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[8] Jewett, H. J.: J. A. M. A., **148:** 187, 1952.

Ten of these 45 patients with known invasive type of bladder cancer of varying degrees of extension are known to have lived five years or longer. This is 22 per cent of the 42 cases. This small series is certainly of no value statistically, it is not reported for that purpose. The reason for this discussion is to simply report that in our opinion good results may be secured by conservative methods in treating these patients. We have tried to combine in a rational manner fulguration, open surgery and radiation and believe that these measures properly applied to most cases of invasive bladder cancer will give as favorable results as more radical procedures There is certainly a place for ureterosigmoidostomy in the treatment of these cases particularly as a palliative measure for a few in which diversion of the urine is advisable. It is desirable that those who have opportunity to promote research in radical surgery for bladder tumor continue to do so. There is reason to believe that much progress may be made in this field. Until we have better and more accurate methods of securing adequate biopsies and thereby are able to determine with more certainty the degree of malignancy and extent of invasion, it would seem reasonable that we should lean towards conservative methods of treatment.

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LOCALIZATION OF RADIOACTIVITY IN THE URINARY BLADDER AND THE REGIONAL LYMPH NODES

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Two of the important factors influencing the prognosis of urinary bladder carcinoma are the type of tumor and the depth of invasion into the bladder wall.[1, 2, 3, 4] These carcinomas range from the noninvasive papillary type through the infiltrating transitional cell, or papillary, cancers to the highly lethal squamous cell variety.

The preferred method of treatment for bladder cancer has been the subject of much dispute for two decades. When the tumor is noninvasive, or only superficially invasive, claims of success by all methods of treatment (transurethral resection, subtotal cystectomy, total cystectomy, cystotomy with fulguration and implantation of radium or radon seeds) seem to be about equal. On the other hand, when the tumor has penetrated deeply into, or through, the detrusor urinae, no method of treatment, developed to date, has proved very satisfactory. There has not been a sufficient number of cases treated by the more radical surgical approach and with an adequate follow-up interval to give additional reason for hope in this type of cancer.

An additional important factor in the prognosis of infiltrating bladder cancer is the relatively high incidence of lymph node involvement present at the time of operation.[5] The route of lymphatic spread in the human is principally to the medial and middle groups of external iliac lymph nodes and less frequently to the hypogastric and common iliac nodes.[6] The hypogastric nodes become more frequently involved when the site of the tumor is on the posterior wall of the urinary bladder.

This paper is a report of animal experiments performed with the hope of gaining information which might prove useful in the therapy of invasive carcinomas.

An attempt to develop a method of delivering an effective dose of radiation limited to the region of a urinary bladder tumor and its lymphatic drainage was made. This method consisted of injecting a radioactive colloidal solution into the wall of the urinary bladder. The colloidal particles are apparently phagocytosed and carried through the lymphatic channels to the regional lymph nodes.[7, 8] If

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This work was done under the supervision of Dr. Marshall Brucer, Chairman of the Medical Division of the Oak Ridge Institute of Nuclear Studies. Miss Germaine Click contributed invaluable technical help and advice.

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the radioactive uptake in the theoretical tumor site and in the lymph nodes is high enough to deliver an effective dose of radiation, a certain amount of palliation should be anticipated

ISOTOPE

Radioactive colloidal gold^{198} was used. Au^{198} may not necessarily be the ideal isotope for clinical application of this method, but it was chosen because of its availability and short half-life which make it a convenient and desirable laboratory isotope Au^{198} has a half-life of 2.7 days It emits beta rays with maximum energy of 0.97 mev. and gamma rays with energy of 0.11 mev. Fifty per cent of the beta rays penetrate only 0.38 mm. and are the primary source of radiation effect. The gamma rays penetrate deeply and are useful for external counting The isotope, obtained from Abbott Research Laboratory of Oak Ridge, Tennessee, is a colloidal solution of particle sizes stated to range from .003 to .004 microns

METHOD

Apparently healthy mongrel dogs were used. The dogs were anesthetized with intravenous sodium pentobarbital, 30 mg./kilo weight. Under sterile conditions a lower abdominal midline incision was made, the urinary bladder was exposed and delivered through the wound. A dose of colloidal Au^{198} was then injected into the muscular layer at the fundus of the bladder, using a lead-protected syringe. The bladder was returned to its position and the abdominal wall was closed.

DOSE

Five millicuries of Au^{198} in 5 cc of N. saline to which 300 turbidity units of hyaluronidase had been added, was injected. Hyaluronidase was added because it has been suggested that it would create a uniform dispersion of the solution

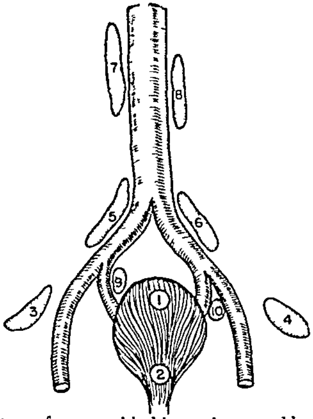

FIG 1 Schematic diagram of urinary bladder and regional lymph nodes of dog indicating areas of assay

throughout the muscular wall,[9, 10, 11, 12, 13] and would probably allow a more effective lymphatic pickup.

AUTOPSY AND ASSAY

The dogs were sacrificed at intervals ranging from five to fifteen days after the injection. Specimens taken from various organs and lymph nodes (fig. 1) were examined for radioactive uptake and histologic changes. The tissue was weighed, digested in nitric acid and diluted to 10 cc volume. The activity in this wet sample was measured with an end-window Geiger-Mueller tube. All figures are recorded as the count per minute per gram of fresh tissue corrected for decay from the time of animal injection.

RESULTS OF ASSAY

Twelve dogs were used. The radiation uptake count in the various organs examined is given to table 1. A high concentration was, of course, found at the site of injection in all the dogs. A fairly consistent uptake with surprisingly high levels was found in the lymph nodes draining the urinary bladder. The nodes along the hypogastric artery, when found, showed the highest activity. The iliac nodes and aortic nodes also showed relatively high concentrations. Very low counts were found in the liver and spleen, indicating that only a minimal amount of Au^{198} entered the blood stream.[14] A certain amount of spillage into the peritoneal cavity undoubtedly occurred during each injection. Free colloidal Au^{198} is very rapidly picked up by the reticulo-endothelial cells of the omentum and can explain the consistently elevated concentration of radioactive material found in the omentum of all of the dogs.[15]

The bladder trigone also had a consistently elevated level of radioactivity, despite the fact that the injection site was several centimeters distant. This may be explained by the rich collateral lymphatic plexus of the urinary bladder as well as the dispersing activity of the added hyaluronidase.

PATHOLOGY

The urinary bladders of four dogs examined 5 days after injection all showed considerable thickening of the bladder wall for several centimeters around the site of injection; this was accounted for by edema and congestion. The areas near the injection site showed early necrosis of the muscle with adjacent fibroblastic proliferation in a loose stroma rich in dilated capillaries (fig. 2) with swollen endothelial cells. There was a thin layer of fibrin on the peritoneal surface with stratification of swollen mesothelial cells. With the exception of swelling of the transitional cells, the mucosa was not remarkable.

Seven dogs examined 13 days and one dog 15 days after injection showed

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[15] Ibid.

TABLE 1. *Radioassay in 12 dogs following injection of radiogold into wall of urinary bladder*

Dog No		110	109	113	114	81	87	92	99	100	103	101	108
Amount of Au^{198}		5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc	5 mc
Time Interval—days		5	5	5	5	13	13	13	13	11	11	11	15
No	Anatomical location												
1	Bladder—fundus	105,100	38,800	72,700	33,000	67,200	54,200	11,100	23,500	21,500	7,200	6,200	95,900
2	Bladder—trigone	59,900	10,600	53,300	370	31,000	760	9,270	1,250	80,600	18,700	11,700	1,290
3	Rt. inguinal L.N.	120	200	15	590	0	*	0	*	365	35	310	0
4	Lt. inguinal L.N.	65	75	140	740	0	60	0	9,310	235	65	80	0
5	Rt. iliac L.N.	5,950	51,600	61,800	8,100	164,000	3,160	10,900	13,190	26,200	22,200	1,210	146,100
6	Lt. iliac L N.	22,000	860,800	21,600	19,800	79,800	131,000	6,320	56,000	91,600	19,800	12,300	2,930
7	Rt. aortic L N.	520	*	371,000	56,200	0	100	31,000	*	*	780	740	58,100
8	Lt. aortic L.N.	1,730	1,890	33,100	0	850	110	19,000	1,290	550	110	1,570	*
9	Rt. hypogastric L.N.	127,300	269,000	*	720	0	*	*	*	*	92,100	370,600	151,100
10	Lt. hypogastric L.N.	121,000	119,000	620	15,600	0	*	*	1,160	*	*	*	10,100
11	Spleen	40	20	30	70	0	0	210	170	210	11,600	0	1,040
12	Lung	1	1	115	90	0	105	0	0	50	290	110	615
13	Heart	0	0	20	15	0	25	0	65	7	150	0	0
14	Liver	65	30	270	100	1,020	100	620	2,020	1,090	700	210	185
15	Kidney	110	10	0	0	30	60	130	60	65	0	215	175
16	Ureter	10	0	16,700	0	0	280	580	1,280	370	*	2,760	0
17	Mesenteric L.N.	*	60	*	110	85	5	310	280	75	240	0	100
18	Omentum	1,225	11,800	2,350	10,800	35,900	580	2,890	5,170	510	2,910	0	15,600
	Background	15	15	16	16	18	15	16	15	15	15	16	16

5 mc. Au^{198} + 300 TR units of hyaluronidase in 5 cc. vol. injected in fundic wall of urinary bladder (dogs) Figures are the count/minute/gram tissue of organ, corrected for decay. 0—Count below background. *—No specimen.

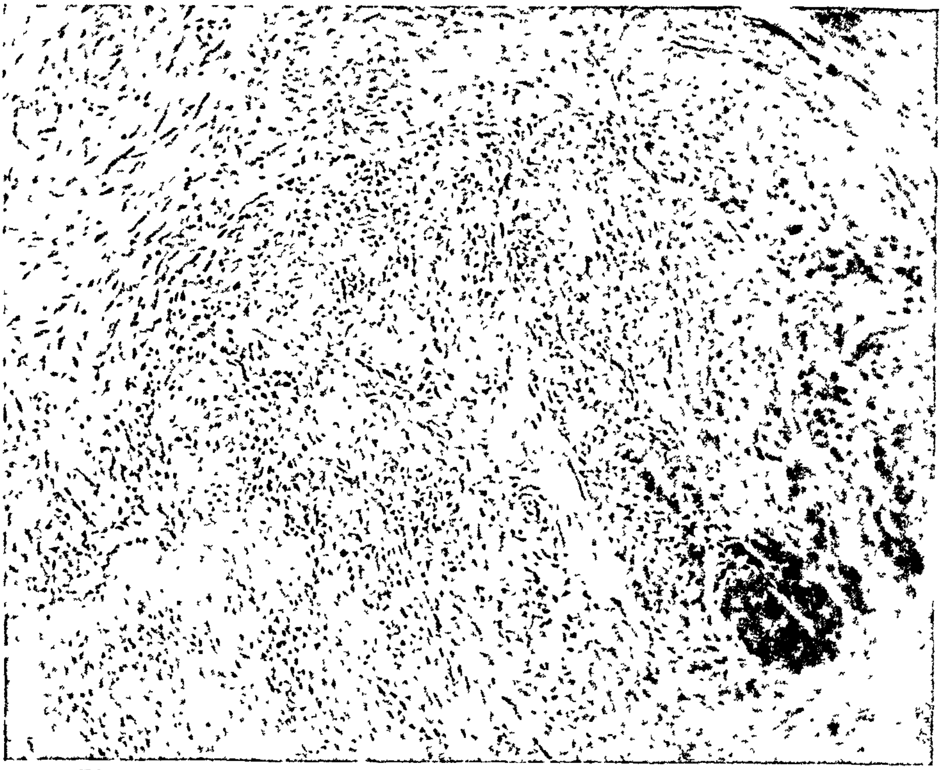

FIG. 2. Photomicrograph of section of urinary bladder (dog 114) injected with Au^{198} showing necrosis of muscle and fibroblastic proliferation.

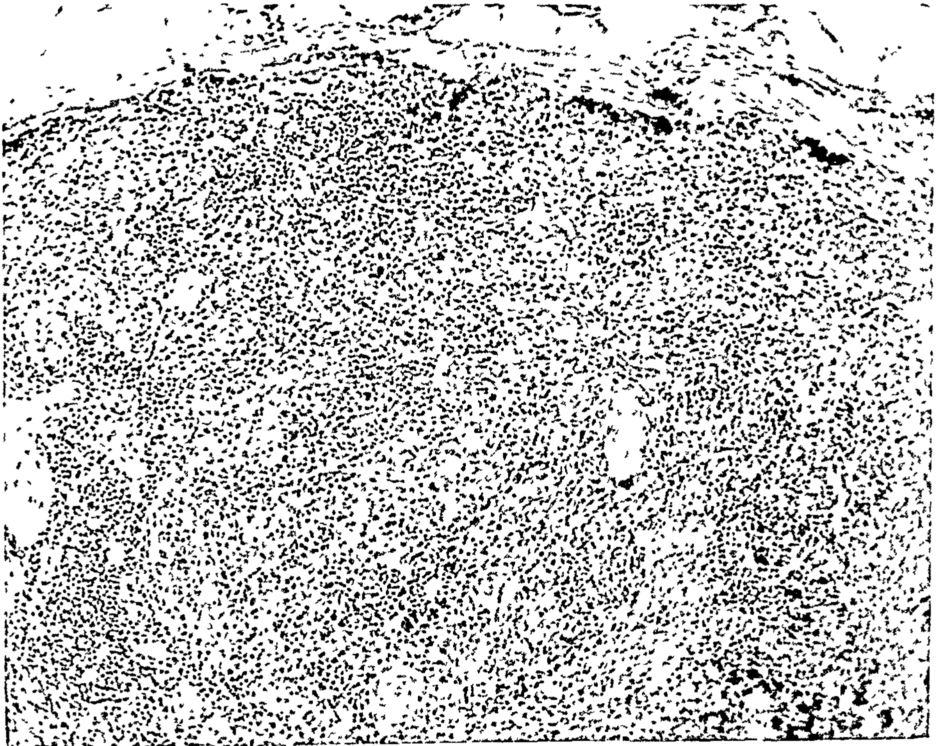

FIG. 3. Photomicrograph of a regional lymph node (dog 100) showing loss of follicles, depletion of lymphocytes, and marked increase in reticulum cells.

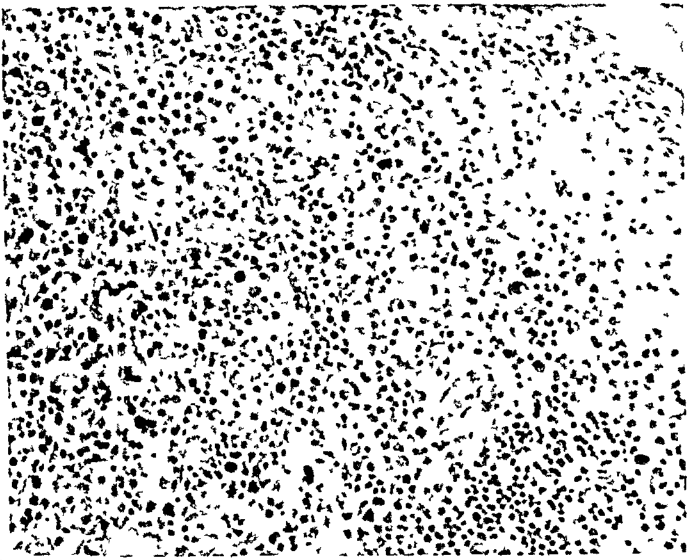

Fig 4 Higher power magnification Note sparsity and pyknosis of lymphocytes increase in reticulum cells Peripheral sinus is obliterated Capsule can be seen in upper right corner

changes in the urinary bladder similar to the first group with the exception that there was less fibrin on the peritoneal surface and rather marked fibroblastic proliferation beneath the peritoneum and in the muscle about the injection site There was minimal mixed leukocytic response

The regional lymph nodes in this latter group were small and could not be found in all cases The histologic findings were qualitatively similar but differed somewhat quantitatively The peripheral sinus was often packed with large pigment-containing mononuclear cells In scattered foci the sinus was replaced by fibrous tissue rich in these pigmented cells Only an occasional node showed marked fragmentation of lymphocytes Plasma cells often made up from about one-sixth to one fourth of the cellular element Follicles with germinal centers were always present, but were apparently decreased in number often showing only one or two in a cross section (figs 3 and 4) No consistent change in blood vessels was noted

The bone marrow was of normal cellularity without detectable maturation abnormalities

DISCUSSION

The deliverance of effective radiation to an inoperable bladder cancer and the regional nodes by conventional radiation therapy has well-known limitations, particularly the damaging effect on adjacent structures The method used in this experiment seems to accomplish well localized effect on the urinary bladder of dogs. At the same time, appreciable radiation is delivered to the regional lymph nodes and a minimal amount of activity is detectable elsewhere in the body. If a higher level dosage of activity were used, one might expect more necrosis at the injection site and higher concentrations of activity in the lymph nodes.

Direct injection of colloidal Au^{198} into tumors has been done with reported success.[16, 17, 18] The major defect in this method has been the uneven dispersion of the radioactive particles, thus failing to deliver uniform radiation. Results will undoubtedly be improved with the development of better techniques.

It is important to remember that these were healthy dogs without carcinoma. In the event the lymphatics are "plugged" with metastatic emboli, it is quite possible that the localization in the lymph nodes would not be so concentrated, or may not have resulted at all. The only way we know to prove this would be by clinical application and trial.

SUMMARY AND CONCLUSIONS

A colloidal solution of Au^{198} was injected intramurally into the urinary bladder of 12 dogs.

Assay and histologic studies were made on dogs sacrificed at various time intervals ranging from five to fifteen days.

Concentrations of radioactivity were found to be consistently high at the site of injection as well as in the trigone of the urinary bladder and in the regional lymph nodes.

Radiogold produced necrosis of the urinary bladder wall at the site of injection. Minor changes were noted in the regional lymph nodes.

These results suggest the possibility of a clinical trial in patients with inoperable bladder carcinoma. Palliation might be afforded these patients if a sufficiently large amount of isotope were utilized creating an effective radiation dose.

[16] Hahn, P. F. and Sheppard, C. W.: Ann. Int. Med., **28**: 598, 1948.

[17] Flocks, R. H. et al.: Loc. cit.

[18] Sherman, A. I., Nolan, J. F. and Allen, W. M.: Loc. cit.

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EXTERNAL URETHRAL MEATOTOMY IN THE FEMALE

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External urethral meatotomy in the female is an easy procedure that requires little time, only a few instruments, and gives excellent results. Complications are infrequent and minimal when they do occur. The indication for this procedure is stricture or stenosis of the female external urethral meatus that does not tolerate comfortably a 30F sound. Meatotomy is done by cutting the posterior lip of the meatus at 6 o'clock (on the face of a clock) at the urethrovaginal juncture. An alternate method is to produce a "fishmouth" pair of incisions at 4 and 8 o'clock (on the face of a clock). Either procedure gives good results

The technique (figs. 1 to 3) consists of injecting about ½ cc of 1 per cent novacain with a sharp, short beveled hypodermic needle at 6 o'clock on the circumference of the meatus. Occasionally it is necessary to "iron out" the urethral meatus with a small sound. After the original injection a small amount of novacain is infiltrated quickly along the floor of the urethra at 6 o'clock and at 5 and 7 o'clock. One half to ¾ cc of 1 per cent novocain is sufficient. As soon as a "bleb" has been raised the rest of the procedure is painless practically. After the sound is removed, a straight hemostat is clamped onto the posterior lip of the meatus, and extending into the urethra from ¹⁄₁₆ to ⅛ inch. It is better to do too little than too much, and occasionally a second procedure will be necessary to secure an adequate opening. This hemostat is left on for 30 seconds to give adequate hemostasis. It is then removed gently and a pair of straight scissors

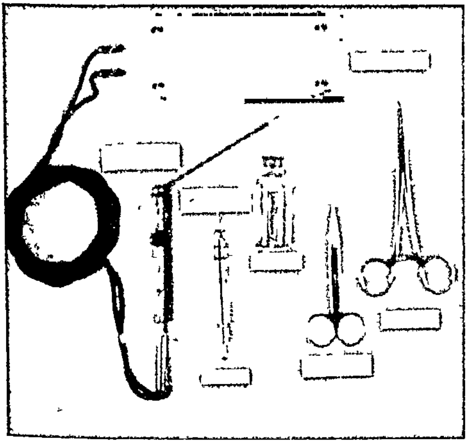

FIG 1 Showing all instruments necessary for procedure

Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26-29, 1953

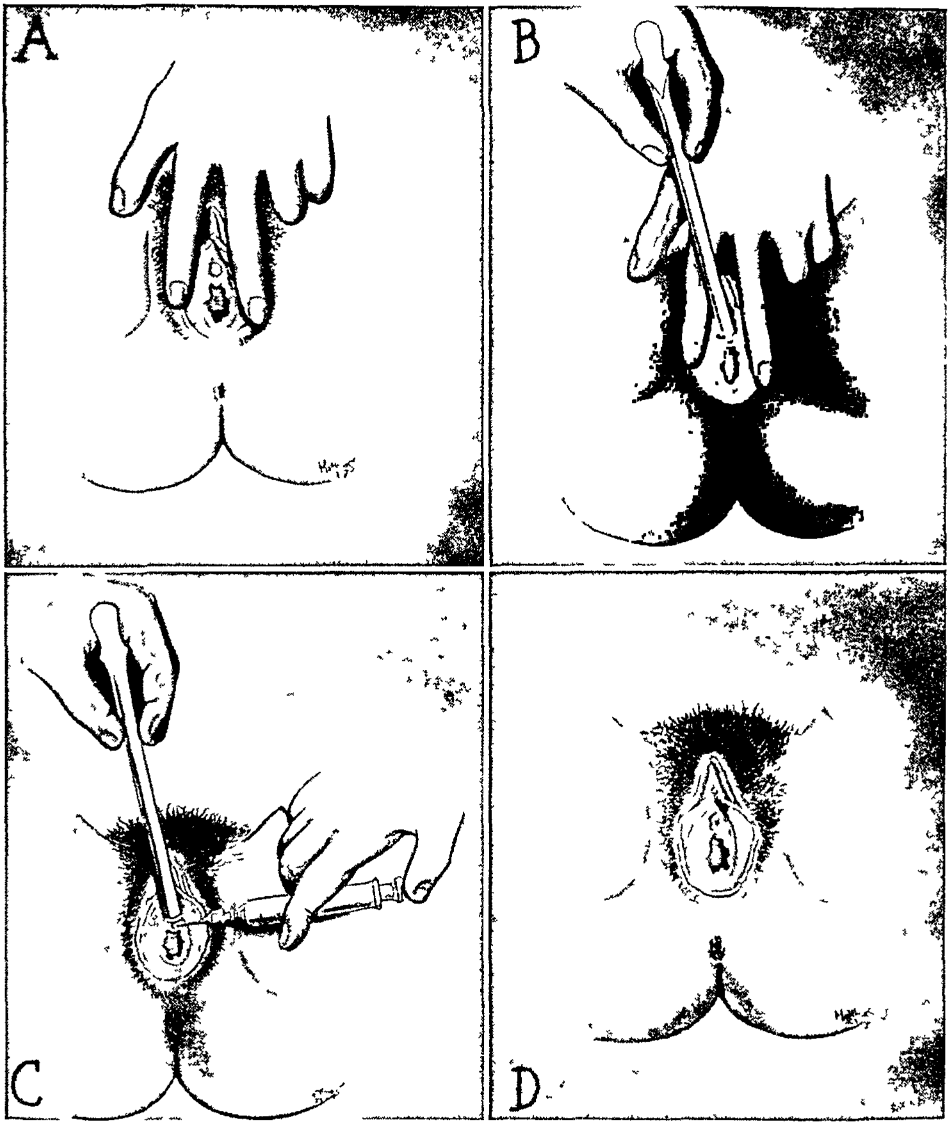

FIG 2 Lithotomy position showing female genitalia and meatal stricture *B*, with a 30F sound inserted through strictured urethra *C*, injection of 1 per cent novocain into posterior lip of meatus *D*, bullous swelling following novocain injection

used to cut along the indentation caused by the hemostat clamping of the tissues. Nos. 24, 26, 28 and 30 sounds are then introduced into the urethra. If there is any "hang" as a sound is passed a small electric cautery tip ("electric needle") is used to enlarge the incision and to secure hemostasis. This is painless provided the steam is not allowed to accumulate around the vulva. An assistant holds the sound while the left forefinger and middle finger of the operator keep the labia apart sufficiently so that no heat or steam can cause discomfort to the patient. Because the small blade used for the electric cautery heats and cools very quickly only a fraction of a second is needed to cut or to coagulate bleeding A 30F sound should pass without any hanging. A small pledget of cotton is inserted

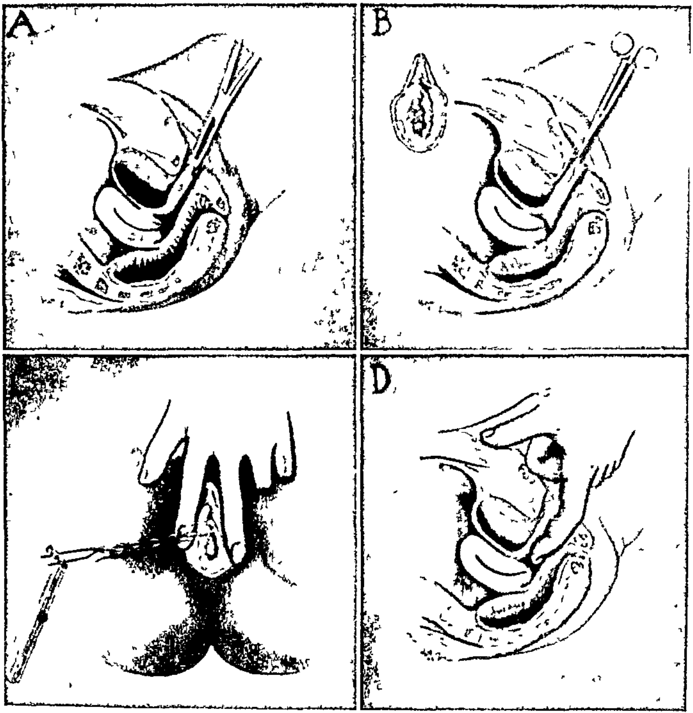

FIG. 3. *A*, sagittal view showing hemostat applied on distal ⅕ inch of posterior lip of meatus *B*, sagittal view showing scissors cutting "clamped" area of posterior lip of meatus. *C*, use of electric cautery tip to control bleeding *D*, sagittal view with finger pressing cotton against cut meatus

into the vagina beneath the cut meatus. The patient is told to remove the cotton before she urinates. If there is any bleeding after urination, she is to re-insert another pledget of cotton and to compress the cotton and meatus against the symphysis by finger pressure. Cotton is kept in as long as there is any bleeding after urination. Some patients will bleed each time they urinate for several days, others will not bleed at all. Still others will have an occasional show of blood and will have to wear a piece of cotton during the next ten days It is possible by this method to control the rare case of hemorrhage that occurs. Sometimes digital compressions of the meatus against the symphysis pubis will be required for a period of three or four minutes before hemostasis is secured. Only twice has the author had to re-inject the area with novocain and fulgurate a particularly troublesome bleeder.

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The microscopic appearance of this type is characterized by reaction without gland formation or with only a tendency to gland formation. In its acute phase, there is moderate to marked edema of transitional mucosa and submucosa, increased vascularity of the mucosa and submucosa with a minimal number of inflammatory cells (fig. 1, *A*). The less acute phase of the granular type shows an increased number of lymphoid elements and less vascularity.

The second type is the acute edematous or the acute polypoid type. This is

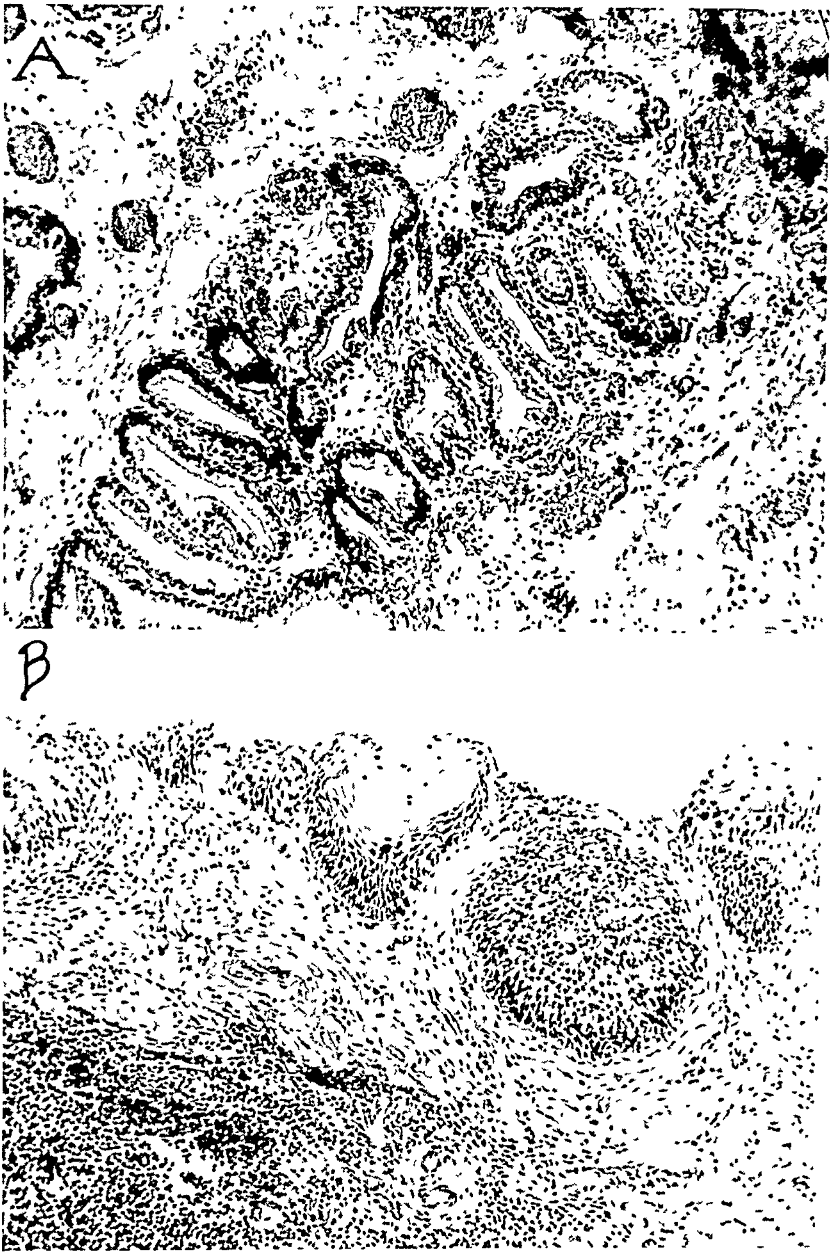

FIG. 2. *A*, section of subacute glandular urethritis showing marked gland formation, increased vascularity with moderate amount of lymphocytic infiltration. *B*, more chronic phase of subacute glandular reaction. Note marked lymphoid reaction, almost gland-like in character, less vascularity, and minimal edema of submucosa.

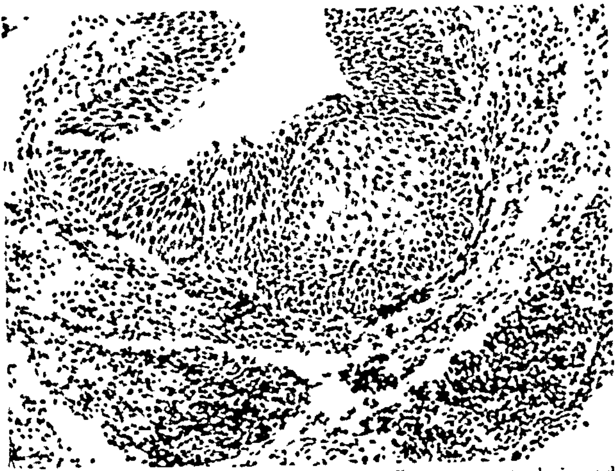

FIG. 3. Section from healed glandular urethritis. Squamous metaplasia and marked lymphoid infiltration are characteristic of type.

a marked inflammatory reaction. Here the mucosa has a polypoid appearance and is diffusely red and edematous. The microscopic section shows marked edema of the mucosa with marked vascularity. Chronic inflammatory elements are absent. Here the glandular structure is evident (fig. 1, *B*).

The third type is the subsiding or subacute change with a polypoid-like appearance, the so-called hyperplastic tab. Here the tab shows a red vascular base with either edema of the tip of the polyps or a complete normal epithelization of it. Some of the tabs are very large, some are only filamentous in appearance. The microscopic section in this type is characterized by gland formation or pseudo-gland formation where in many instances the lumina are filled with acidophilic mucin. In the more acute reaction there is edema of the mucosa, moderate to severe edema of the submucosa, the vessels of the mucosa are both large and small, and there is a minimal lymphoid infiltration (fig. 2, *A*). The less acute reaction is manifested by less edema and an increase in the amount of lymphocytic infiltration even to the appearance of lymph gland formation (fig. 2, *B*).

The fourth type or the healed stage shows the polypoid structure entirely epithelized with normal-appearing mucosa or abnormally pale mucosa. On section there is seen squamous metaplasia with minimal to no edema of the mucosa and submucosa and a marked lymphoid infiltration with a minimal number of vessels (fig. 3).

RESULTS OF THE STUDY

The 51 patients who were treated locally received dilatation and the gamut of local administration including the following: ¼– 2 per cent $AgNO_3$; ½– 5 per cent Protargol; Furacin 1:2 and 1:6 dilution; and a 1 per cent Terramycin solution.

Seventeen cases were classified as granular, and of these only four failed to clear completely as to the appearance of the urethra, symptoms, and recurrences over a 1-year period. This group received an average of 5 treatments per patient, a figure somewhat above the actual average because one patient received a total of 19 treatments. Of the four who failed, one patient had diabetes and one other had chronic pyelonephritis.

Four cases were of the acute glandular type; one cleared completely and the other three subsided with only minimal evidence of the severe reaction after three treatments.

Twenty-eight patients were described as the subacute glandular type. Of this

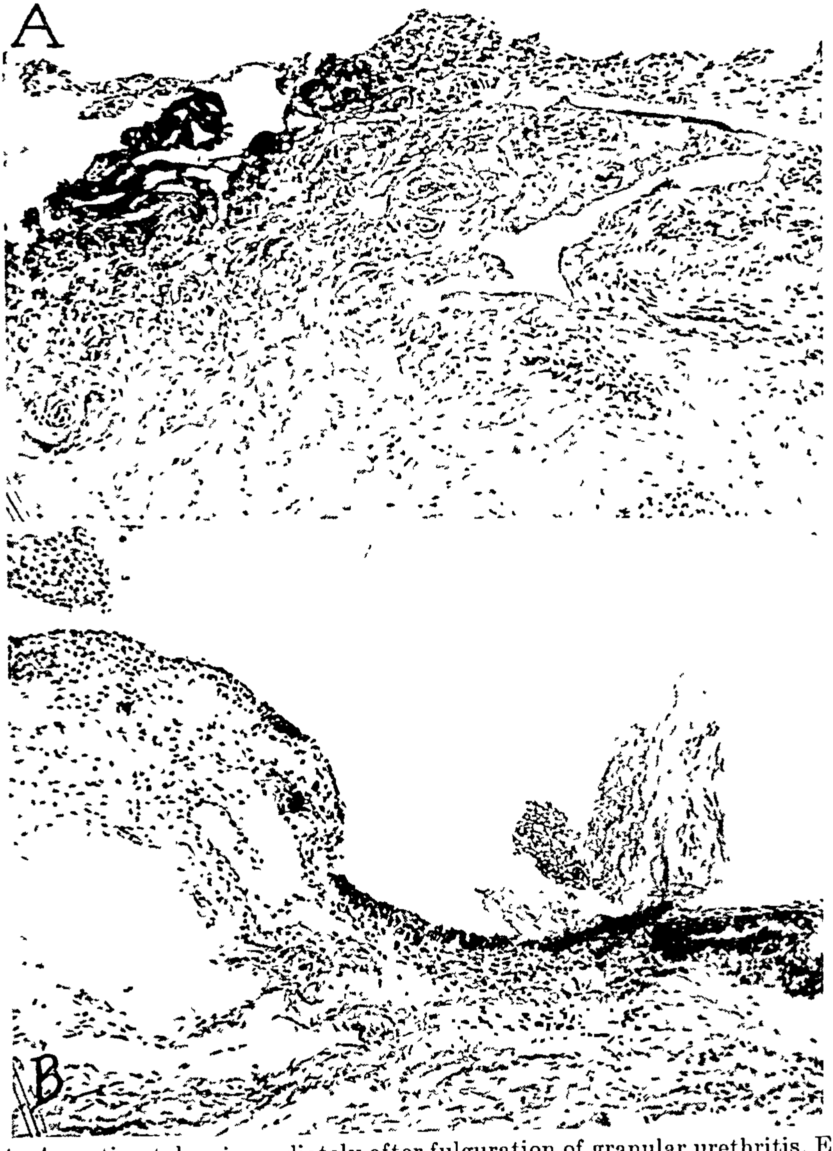

Fig. 4. *A*, section taken immediately after fulguration of granular urethritis. Extensive destruction of tissue is evident. *B*, urethra that had been fulgurated in granular stage 6 months previously.

group, in only 3 cases did the urethra return to normal, and these were described as small filamentous tabs. This group received an average of eight treatments per patient.

Two patients were classified in the healed group. One of these showed no change, the other cleared with local medication and estrogen suppositories.

A detailed endoscopic description of each of the 25 patients on whom biopsies were taken with the pathologist's description of the biopsy was compiled. The conclusions were those reached in the classification, and because it entails seven pages is not included.

Having established the comparison between the endoscopic appearance and the pathological specimen we then wanted to determine what types of responses might be anticipated from the two basic forms of therapy on each of the types of urethritis by taking biopsies immediately after treatment. We used 2 per

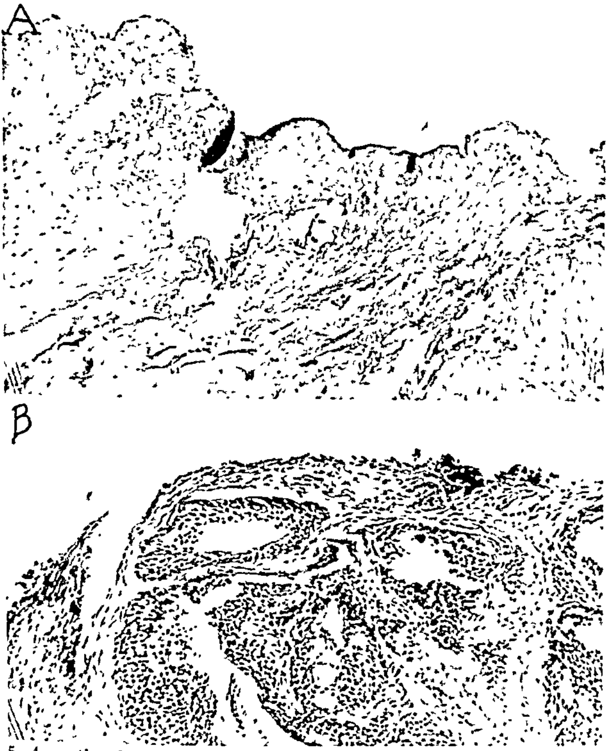

FIG. 5. *A*, section from acute glandular urethritis immediately after fulguration. Extensive destruction again noted. *B*, biopsy after application of 2 per cent silver nitrate on subacute glandular urethritis. Silver stain may be seen over tips of glands.

cent silver nitrate for maximum penetration and staining. The results are included in the discussion.

DISCUSSION

The granular stage shows an increased vascularity with minimal inflammatory cells and no metaplasia but, most important, no glands or only a tendency to form glands. This type responds to almost any form of therapy, drugs in the young and mild local therapy in the older patient. These patients need not be subjected to urethral fulguration. Figure 4, *A* shows a section from a granular urethra after fulguration. One notes destruction of the mucosa and submucosa, leaving only charring and muscle fibers. While the mucosa will eventually return to normal, figure 4, *B* shows granular urethra 6 months after fulguration; the morbidity required is rarely necessary. It is evident also that a local medication can come in contact with the mucosa sufficiently to remove the granular reaction. The acute glandular type is an acute reaction and should be treated as such with antibiotics and mild local therapy. Our clinical experience shows that the majority will clear, but if they persist in the subacute form they then should be treated as such. In figure 5, *A* the excessive destruction caused by fulguration is evident and generally results in more morbidity than necessary for this type of pathological change.

With the subacute glandular reaction the response to local medication is poor due to the obvious difficulty of any medication reaching beyond the tips of the glands. Figure 5, *B* shows sections taken after the application of 2 per cent silver nitrate on a swab revealing that the medication reaches only a small portion of the tissue taken for biopsy. Figure 6 shows the good results by fulguration without extensive destruction of the musculature.

The healed, or chronic, stage with squamous metaplasia and marked infiltra-

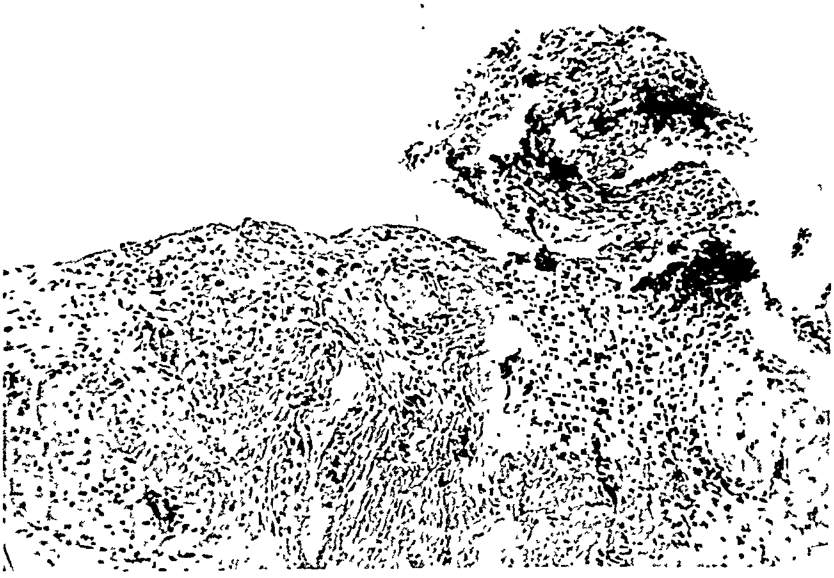

FIG. 6. Post-fulguration biopsy of subacute glandular urethritis showing destruction of glandular elements without extensive destruction of submucosa.

tion of lymphoid tissue usually is resistant to any form of local therapy and is a questionable source of irritation and reflected pains. We feel that patients with this condition should not receive local therapy unless the symptoms per se can be shown definitely to be referred from the urethra[12] and then they should be treated by fulguration or resection

CONCLUSION

Correlation has been shown between the gross appearance of urethritis and the microscopic classification of biopsies taken from the lesion

An adequate number of patients presented show this correlation

The mild reaction and the more severe acute reaction in young women should be treated conservatively by local therapy.

More common are those with large tabs which failed to respond in general to local therapy and who should be treated by fulguration

The chronic, or healed, stage usually being nonamenable to local therapy, should be treated by fulguration or resection.

We want to express our thanks to the Department of Surgical Pathology, Washington University, and particularly to Dr. Vernon Pettit, who reviewed all of our tissue specimens

[12] Powell, E M , and Wattenberg, C A To be published

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PEYRONIE'S DISEASE: CORTISONE-HYALURONIDASE-HYDROCORTISONE THERAPY

HENRY BODNER, ALLAN H. HOWARD AND JOSEPH H. KAPLAN

Since the original description by Peyronie in 1743, the disease which bears his name has been described, variously, as follows: Fibrous cavernositis, fibrous plaques of the penis, chronic cavernositis, fibrous sclerosis and plastic induration of the corpora cavernosa. This preliminary report deals with the results of therapy with adreno-cortical hormones in 16 patients with Peyronie's disease and one additional case in which hyaluronidase alone was used.

The etiology, pathology, symptoms and treatment of Peyronie's disease has been adequately reviewed by Dr. Wesson[1] and by Dr. Burford[2] in the more recent medical literature. We shall, therefore, in this presentation emphasize the therapy in plastic induration of the corpora cavernosa. Wesson stated that "any phallus when turgid or partially so, that has a tendency to be deflected in any part away from a mathematical straight line is a potential case of plastic induration." Pain with erection is a symptom of alarming importance to the average egoistic male. Due to the necessity of frequent daily handling of the penis, the deviation from the normal is readily ascertained. Therefore, curvature of the penis, pain with erection and palpation of the fibrous plaques in the penis are the symptoms of primary importance which stimulate the patient to seek medical aid and are signs and symptoms evaluated before and after therapy.

The treatment of plastic induration of the corpora cavernosa as suggested in the literature has been extremely varied. Topical applications of iodine, mercury, camphor, iodoform; iodides and arsenic internally, massive doses of vitamin E; fibrolysin injected hypodermically into the lesion; diathermy, electrolysis and ultra-violet light; x-ray therapy; radium therapy; surgical excision of the fibrous plaque; and combination of the aforementioned have all been used. It is a foregone conclusion that, in any condition in which a varied number of therapeutic agents are used for therapy, that each method in itself is ineffective in providing a desired result.

Scott[3] in a series of 33 cases reported that slightly over 80 per cent of patients showed at least some response to tocopherol therapy. In Burford's series of 47 cases, 72.4 per cent were either cured or improved by radium therapy. Lowsley concludes that Peyronie's disease is curable by surgery if the plaque formation is not too extensive. He condemns radiation.

This study includes 17 patients and was started in March 1951. There were two patients in the third decade, three patients in the fourth decade, ten patients in the fifth decade and two patients in the sixth decade. The youngest patient was 35 years of age and the oldest 66. In this group of 17 patients, 12 complained

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

[1] Wesson, M. B.: Peyronie's disease (plastic induration): Cause and treatment. J. Urol., **49:** 350–356, 1943.

[2] Burford, C. E., Glenn, J. E. and Burford, E. H.: Fibrous cavernositis: Further observation with report of 31 additional cases. J. Urol., **56:** 118–120, 1946.

[3] Scott, William Wallace: Ann. New York Acad. Sc., **52:** 390–396, 1949.

TABLE 1 *Results of treatment with cortisone, hydrocortisone, cortisone and hyaluronidase, and hyaluronidase in 17 cases of Peyronie's disease*

DRUG EMPLOYED	NUMBER OF CASES	GOOD	RESULTS IMPROVED	POOR
Cortisone	8	3	5	0
Hydrocortisone	3	1	2	0
Cortisone and hyaluronidase	5	2	2	1
Hyaluronidase	1	0	0	1
Total	17	6	9	2

TABLE 2 *Effect of cortisone, cortisone and hyaluronidase, hydrocortone and hyaluronidase on the curvature of penis produced by Peyronie's disease in 15 cases*

DEGREE OF CURVATURE	NUMBER OF CASES	GOOD	RESULTS IMPROVED	POOR
Mild	6	2	0	4
Moderate	5	1	2	2
Severe	4	2	1	1
Total	15	5	3	7

TABLE 3 *Effect of cortisone, cortisone and hyaluronidase, hydrocortone and hyaluronidase on pain in penis produced by Peyronie's disease in 12 cases*

DEGREE OF PAIN	NUMBER OF CASES	GOOD	RESULTS IMPROVED	POOR
Mild	2	1	1	0
Moderate	6	6	0	0
Severe	4	2	2	0
Total	12	9	3	0

of painful erections and 15 were aware of curvature of the penis during erections A plaque, palpated in all 17 patients, varied in size from about 1½ x 1 cm to involvement of the entire dorsum of the penis Three patients had been treated with alpha tocopherol, two had received x-ray therapy, one diathermy, one radium and one patient had been treated with surgery plus estrogens The patients in this study were divided into the following three groups (tables 1, 2, 3): those treated with cortisone,[4] cortisone and hyaluronidase[5] and hydrocortisone[6] One patient, in addition was treated with hyaluronidase alone A course of therapy arbitrarily consisted of 25 mg of the selected drug once weekly with ½ cc of 1 per cent novocaine for a total of 10 weeks In the 5 patients who received hyaluronidase in addition, 150 turbidity reducing unit dosage was used Upon the completion of one course of therapy, for the following 30 days, the plaque was evaluated from the standpoint of pain, curvature and size. Patients were selected for more than one course of therapy if the plaque or the symptoms it produced were unchanged or only slightly improved. In no instance was more than four courses of therapy given. It was our impression that 25 mg. of cortisone or hydrocortisone given at weekly intervals would not produce any untoward reactions. Six patients had been treated with one course, 8 patients with two courses, one with three courses and 2 patients with four courses of therapy.

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[4] Giles, R G Urol & Cutan Rev , 51 399, 1947

[5] Lowsley, O S and Boyce W H Further experiences with an operation for cure of Peyronie's disease J Urol , 63: 888–899, 1950 Lowsley, O S and Gentile, A J Urol , 57 552, 1947

[6] Baker, Roger, Duncan, Govan and Huffner, J Inhibitory effect of cortisone on strictures of urologic tract Surg , Gynec & Obst , 95: 446–451, 1952

Whenever possible the size of the plaque was measured and recorded. An attempt was made also to evaluate the consistency of the plaque insofar as firmness was concerned, that is, if a plaque felt more pliable after therapy. The duration of the symptoms of these patients when first reporting for care was consistent with that in the literature.

A 10 cc Luer-Lok syringe on a 21 or 22 gauge needle was employed to inject the medication into the plaque. The forefinger and thumb of the left hand grasped the plaque and the needle was then inserted directly into the middle of the lesion. In most instances it was necessary to exert a great deal of pressure on the piston of the syringe to inject the medication into the plaque. On some few occasions it was necessary to begin therapy in the lateral aspect of the plaque, since it was impossible to inject the drugs directly into the lesion. After two or three treatments, less pressure was required for injection.

The results in those treated with cortisone alone were good in three and improved in five. In those treated with cortisone plus hyaluronidase the results were good in two, improved in two and poor in one. In those treated with hydrocortisone the results were good in one and improved in two. The patient treated with hyaluronidase alone showed no change. In the entire series irrespective of the type of medication used, the results are as follows: Good in six, improved in nine and poor in two. One patient treated with hyaluronidase alone stated there was no improvement whatsoever. One patient classified as a failure had marked decrease in pain, but there was no change in the amount of curvature and he was still unable to have intercourse. Therefore, with evaluation from the standpoint of the pain, curvature and size of the plaque, we may conclude that we have demonstrated improvement in 16 out of 17 patients. Of the two patients classified as poor results, one had two courses of therapy and the other had one course of therapy.

Statistics in a small series of cases are inconclusive. However, from preliminary investigation it is apparent that adrenocortical hormones, cortisone and hydrocortisone are effective agents in the treatment of Peyronie's disease. Hydrocortisone is, perhaps, even more effective than cortisone if we may base this conclusion on the results obtained in one case in which the fibrous plaque completely disappeared after three injections of 25 mg. each of hydrocortisone. Hyaluronidase did not effect any change in the size of the plaque in the one case in which it was exclusively used. There were no toxic effects noted in any of the patients included in this study. One-half of the patients in this series had poor response to previous types of therapy. However all of these patients improved on cortisone and hydrocortisone therapy.

It was our impression that the patients who were subjected to three and four courses of therapy invariably demonstrated better results insofar as curvature, pain and the size of the plaques. One cubic centimeter (25 mg.) of hydrocortisone with ½ cc of novocain injected directly into the fibrous plaque for a period of 10 to 40 consecutive weeks is the recommended therapy. Hyaluronidase should also be used.

Further study with a larger number of patients over a longer period of time is warranted.

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TERATOMA TESTIS: REPORT OF 100 CONSECUTIVE CASES

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This study has been undertaken to evaluate clinically an open series of 100 consecutive malignant tumors of the testicle seen at Letterman Army Hospital between the years 1945 and 1952, inclusive. Testicular tumor presents a much higher incidence of admission in military hospitals than in civilian institutions. During the 8-year period studied, testicular malignancy represented .007 per cent of all admissions to the hospital, 3.5 per cent of all malignancies, and 36 per cent of all malignant urogenital neoplasms.

CLASSIFICATION

Friedman and Moore's[1] pathological classification of teratoma testis has been used in this study. The results are shown in figure 1. Multiple sections were taken of all tumors and when mixed elements were found the tumor was classified under its most malignant character, disregarding the most prevalent cell type. In many cases thorough study of "pure" seminoma has revealed other elements. It is noteworthy that metastatic lesions found at autopsy frequently present a more malignant cell pattern than the primary. The distribution in this series is somewhat at variance with Friedman and Moore's study of 922 cases, embryonal carcinoma representing 48 per cent of our series whereas it was found in only 19 per cent of theirs.

DISTRIBUTION

The average age in the entire series was 28.7 years, the youngest being 16 and the oldest 53 (table 1). All cases occurred in soldiers. The average age of the seminoma patients was slightly higher than in the other groups. The right testis was involved in 56 and the left in 44. One case was bilateral; the second tumor, a teratocarcinoma, developing 6 years after the first which was an embryonal carcinoma. One case occurred in a Negro. The low incidence of this lesion in Negroes was stressed by Merren, Vest and Lupton.[2]

Two tumors occurred in undescended testes and two were found in previously operated cryptorchid testes. The relationship of malignancy to maldescent has been the subject of considerable controversy, but it is our impression that arrested descent is not a predisposing factor in development of testicular tumor. Carroll,[3] in his scholarly statistical study of this subject, concluded that the alleged higher incidence of testicular tumor in cryptorchids cannot be accepted and should not affect the decision for orchiopexy or orchiectomy.

SYMPTOMATOLOGY

There are no pathognomonic symptoms. Painless swelling is the most common symptom. This complaint was presented on admission by 67 patients. The swell-

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

[1] Friedman, N. B. and Moore, R. A.: Mil. Surg., **99:** 573, 1946.

[2] Merren, D. D., Vest, S. A. and Lupton, C. H., Jr.: J. Urol., **65:** 128, 1951.

[3] Carroll, W. A.: J. Urol., **61:** 396, 1949.

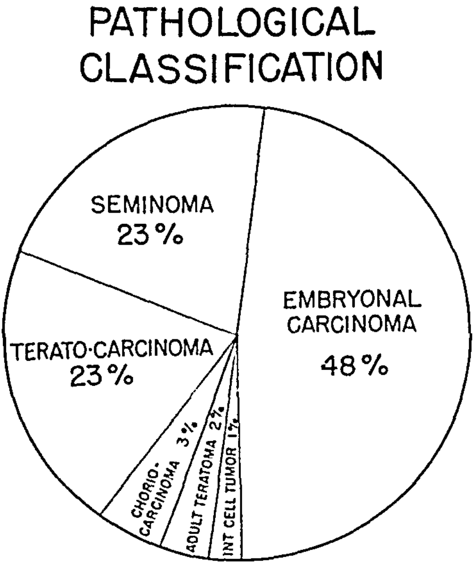

Fig 1

Table 1 *Age distribution*

Diagnosis	Average age in years	Number between 20–30	Number between 30–40	Minimum and maximum
Seminoma	31.2	5	15	19–45
Embryonal carcinoma	29.3	25	21	21–53
Chorio carcinoma	30	1	2	24–30
Terato carcinoma	26	14	6	16–41
Teratoma-adult	30	1	1	28–32
Interstitial-cell tumor	21	1	0	21
Entire group	28.7	47	45	16–53

ing may vary from a tiny irregular nodule to a large firm uniform tumor. The conformation of a tumor does not suggest the histological diagnosis, nor does its size affect the prognosis.

A history of trauma to the involved orchid was elicited from 19 patients. The role of trauma in relation to etiology is uncertain. It may, however, call to the attention of the patient a pre-existing swelling.

The initial symptoms may be associated with metastasis. Six of our patients presented themselves with metastatic symptoms. Gynecomastia should lead one to suspect a hormone producing tumor, and when associated with a testicular neoplasm it is an unfavorable prognostic finding except in the case of interstitial cell tumor. Table 2 lists the presenting symptoms in this series.

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TERATOMA TESTIS: REPORT OF 100 CONSECUTIVE CASES

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This study has been undertaken to evaluate clinically an open series of 100 consecutive malignant tumors of the testicle seen at Letterman Army Hospital between the years 1945 and 1952, inclusive. Testicular tumor presents a much higher incidence of admission in military hospitals than in civilian institutions. During the 8-year period studied, testicular malignancy represented .007 per cent of all admissions to the hospital, 3.5 per cent of all malignancies, and 36 per cent of all malignant urogenital neoplasms.

CLASSIFICATION

Friedman and Moore's[1] pathological classification of teratoma testis has been used in this study. The results are shown in figure 1. Multiple sections were taken of all tumors and when mixed elements were found the tumor was classified under its most malignant character, disregarding the most prevalent cell type. In many cases thorough study of "pure" seminoma has revealed other elements. It is noteworthy that metastatic lesions found at autopsy frequently present a more malignant cell pattern than the primary. The distribution in this series is somewhat at variance with Friedman and Moore's study of 922 cases, embryonal carcinoma representing 48 per cent of our series whereas it was found in only 19 per cent of theirs.

DISTRIBUTION

The average age in the entire series was 28.7 years, the youngest being 16 and the oldest 53 (table 1). All cases occurred in soldiers. The average age of the seminoma patients was slightly higher than in the other groups. The right testis was involved in 56 and the left in 44. One case was bilateral; the second tumor, a teratocarcinoma, developing 6 years after the first which was an embryonal carcinoma. One case occurred in a Negro. The low incidence of this lesion in Negroes was stressed by Merren, Vest and Lupton.[2]

Two tumors occurred in undescended testes and two were found in previously operated cryptorchid testes. The relationship of malignancy to maldescent has been the subject of considerable controversy, but it is our impression that arrested descent is not a predisposing factor in development of testicular tumor. Carroll,[3] in his scholarly statistical study of this subject, concluded that the alleged higher incidence of testicular tumor in cryptorchids cannot be accepted and should not affect the decision for orchiopexy or orchiectomy.

SYMPTOMATOLOGY

There are no pathognomonic symptoms. Painless swelling is the most common symptom. This complaint was presented on admission by 67 patients. The swell-

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

[1] Friedman, N. B. and Moore, R. A.: Mil. Surg., **99**: 573, 1946.

[2] Merren, D. D., Vest, S. A. and Lupton, C. H., Jr.: J. Urol., **65**: 128, 1951.

[3] Carroll, W. A.: J. Urol., **61**: 396, 1949.

TABLE 4. *Survival of those showing metastasis on admission*

DIAGNOSIS	TOTAL		ALIVE		DEATHS		LESS 1 YEAR		1-2 YEARS		2-3 YEARS		3-4 YEARS		4-5 YEARS		OVER 5 YEARS	
	No	%	No	%	No	%	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Seminoma. . .	8	35	8	100	0	0	4	0	0	0	1	0	1	0	1	0	1	0
Embryonal carcinoma . .	17	35	6	35	11	65	1	7	1	4	0	0	0	0	0	0	4	0
Chorio-carcinoma . .	2	67	0	0	2	100	0	2	0	0	0	0	0	0	0	0	0	0
Terato-carcinoma. . . .	11	48	7	64	4	36	3	2	1	2	2	0	0	0	0	0	1	0
Teratoma—adult .	1	50	0	0	1	100	0	1	0	0	0	0	0	0	0	0	0	0
Interstitial-cell tumor	0	0																
Total	39	39	21	54	18	46	8	12	2	6	3	0	1	0	1	0	6	0

site of transection. Eight seminomas, 11 teratocarcinomas, 17 embryonal carcinomas, 2 choriocarcinomas and one adult teratoma comprised this group.

Of the 61 patients who were free of demonstrable metastasis on admission, 26 later developed metastasis after treatment. Of this number 23 are known to be dead. Inguinal and femoral node metastasis occurred in only one case, that in a surgically corrected cryptorchid with extension of the tumor to the scrotal tissues.

Metastasis occurs by way of the lymphatics as a general rule, to the periaortic, mediastinal and supraclavicular nodes. Choriocarcinoma usually spreads by blood stream invasion. Pulmonary metastases are common but other visceral spread occurs only infrequently except as a terminal manifestation. Bony metastases are uncommon.

SURVIVAL

The patients in this series have been followed from 1 month to 8 years. Three have been lost to follow-up. Of the remainder 60 are alive, but 5 of these, one teratocarcinoma and 4 embryonal carcinomas, have metastasis. Thirty-eight patients are alive and well 2 years after treatment, and 24 over 5 years. Of the 60 living patients, 21 had metastasis on admission (table 4). Of the 37 who died, 30 or 81 per cent succumbed within the first 2 years. Metastasis developed in 26 who were free of metastasis on admission, and only three of this group are now alive, one 7 years, one 20 months, and the third 11 months. The last is at present hospitalized with extensive metastasis.

Survival is much higher with seminoma, 90 per cent of our cases being alive. The survival rates of embryonal carcinoma and teratocarcinoma are 44 per cent and 48 per cent respectively in this series. The 3 cases of choriocarcinoma died within 6 months. One of the 2 adult teratomas died within one year with autopsy findings of choriocarcinoma; the other is alive and well over 5 years (tables 5 and 6).

TABLE 5. *Total dead*

DIAGNOSIS	DEATHS		DIED LESS 1 YR.		DIED IN 1-2 YRS		DIED IN 2-3 YRS		DIED IN 3-4 YRS		DIED IN 4-5 YRS		DIED AFTER 5 YRS	
	No	%	No	%	No	%	No.	%	No.	%	No	%	No	%
Seminoma	2	10	0	0	1	50	0	0	1	50	0	0	0	0
Embryonal carcinoma	20	44	9	45	7	35	3	15	1	5	0	0	0	0
Chorio-carcinoma	3	100	3	100	0	0	0	0	0	0	0	0	0	0
Terato-carcinoma	11	48	3	27	6	55	1	9	1	9	0	0	0	0
Teratoma—adult	1	50	1	100	0	0	0	0	0	0	0	0	0	0
Interstitial-cell tumor	0	0												
Total	37	38	16	43	14	38	4	11	3	8	0	0	0	0

TABLE 6. *Overall survival*

DIAGNOSIS	ALIVE		DEATHS		ALIVE C̄ METASTASIS	ALIVE LESS 1 YR	ALIVE 1-2 YRS	ALIVE 2-3 YRS	ALIVE 3-4 YRS.	ALIVE 4-5 YRS	ALIVE OVER 5 YRS.	NOT FOLLOWED
	No	%	No	%								
Seminoma	20	90	2	10	0	4	3	4	3	3	3	1
Embryonal carcinoma	26	56	20	44	4	3	3	0	0	1	19	2
Chorio-carcinoma	0	0	3	100								0
Terato-carcinoma	12	52	11	48	1	7	1	2	0	1	1	0
Teratoma—adult	1	50	1	50	0						1	0
Interstitial-cell tumor	1	100	0	0			1					
Total	60	62	37	38	5	14	8	6	3	5	24	3

Of the 8 patients undergoing retroperitoneal node dissection, five had positive nodes. Of these five all are alive, two with extensive metastasis at this time. Two of those living were seminomas. The fifth, a teratocarcinoma, has been followed less than a year since operation. Of the three with negative nodes, two, both seminomas, are dead from later metastasis. All 8 patients received postoperative radiation.

Our overall survival rate of 62 per cent is relatively high, but 22 of the living cases, five showing metastasis at this time, have been followed less than 2 years.

TREATMENT

Ninety cases were treated by simple orchiectomy and postoperative radiation. Orchiectomy is performed by ligation and transection of the cord in the inguinal canal at the level of the internal ring with delivery of the testis through the inguinal wound. Eight patients had the Chevassu operation, all eight receiving postoperative radiation. Two patients were admitted in a terminal state and received no therapy. No patient received preoperative radiation.

The histological classification of a testicular tumor and the location and extent of metastases are of vital importance in planning a course of radiation therapy and in predicting the probable results of such treatment.

Pure seminoma (probably rare) with limited involvement of lymph nodes along the iliac arteries and aorta is most amenable to radiation treatment, and excellent results may be expected in a high percentage of cases. The seminoma, although histologically undifferentiated and anaplastic has a relatively long natural history and is the most sensitive of the tumors of the testis. It is believed that a tissue dose of 1000r administered in 2 weeks' time is lethal to the cells of pure seminoma; however, in order to insure a better margin of safety the tumor dose should probably never be less than 2000r in 3–4 weeks.

Malignant tumors of the testis, other than seminoma, are more resistant to radiation. The lethal dose for these tumors is estimated to be 4000r or more. This approaches the tolerance of surrounding normal tissue, and serious post-irradiation effects can be anticipated if that dosage, given in a period of 3–4 weeks, is exceeded.

When metastases are confined to the retroperitoneal lymph nodes below the level of the renal pedicles, a course of irradiation in which a tumor dose of 2500–3000r (2000r in seminoma) is delivered through anterior and posterior opposing fields in a period of 3–4 weeks may be considered satisfactory treatment. When metastases are known to be in nodes at the level of the renal pedicles the question of prophylactic treatment of the mediastinum and left sternoclavicular region arises. The general condition of patients who have received a full course of radiation treatment to the retroperitoneal lymph nodes is occasionally such that they cannot very well tolerate a full course of treatment to the mediastinum and the decision is frequently made to treat only the left sternoclavicular area initially and the mediastinum at a later date. Rarely does a patient with mediastinal lymph node involvement survive very long in spite of heavy doses of radiation. The exceptions, however, make the effort worthwhile.

In calculating tumor dosages to the retroperitoneal nodes along the aorta and iliac arteries, it must be remembered that they lie at varying depths from the surface of the abdomen and/or back. Adequate, but not excessive, dosages must be delivered to the nodes at each level.

X-rays in the supervoltage range (1000 KV) offer some advantage over radiations produced at 250 KV in that tumor doses may be delivered in a shorter period of time without increasing the danger to skin and other normal tissue.

TREATMENT OF LATE METASTASES

Metastases which develop after treatment are usually resistant to all types of therapy. Some palliation may be obtained with radiation. Two cases, both teratocarcinoma, were treated by lobectomy for removal of a solitary pulmonary metastasis. One of these patients is alive 32 months since this operation with no other evidence of metastasis.

In two patients with extensive metastasis the opposite normal testis was removed because of favorable response with this procedure reported by Shivers,[5]

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[5] Shivers, C. H. deT.: J. Urol., 54: 539, 1945.

McClelland,[6] Saleely,[7] and others,[8] but in neither instance was the fatal outcome delayed.

Nitrogen mustard, ACTH, cortisone and estrogens, have all been used in terminal cases with equivocal results in some patients and none has shown more than temporary improvement.

COMMENTS

It is our belief that routine retroperitoneal node dissection in testicular tumor has not materially altered the survival rates. When one considers the high incidence of contralateral node involvement, the technical difficulty of exposing the "critical area" in the region of the renal pedicles without relying on heroic incisions, and the likelihood of pre-existing embolic seeding of mediastinal and supraclavicular nodes, the justification for subjecting patients to the ordeals of such a major surgical procedure seems hardly warranted. As a policy, we recommend the Chevassu operation only when cord structures histologically show tumor invasion without evidence of any other metastases and when the tumor type is other than seminoma, interstitial cell tumor or choriocarcinoma. All tumors are postoperatively radiated except the rare interstitial cell tumor which is clinically benign.

The critical period in testicular tumors is the first two years. Well over 90 per cent surviving this period are "cured." The demonstration of metastasis on admission does not necessarily offer a hopeless prognosis. Of our 39 cases fitting this description, 21 are alive, 11 over 5 years. Conversely, metastasis appearing after treatment offers a very serious outlook, 23 of our 26 patients in that category having died within 2 years.

The major hope of reducing the high mortality of this tumor lies not in more refined surgical techniques or in more powerful radiation devices, but in earlier recognition of the lesion.

[6] Mc Clelland, J. C.: J. Urol., 49: 31, 1943.
[7] Saleely, E. R.: Ann. Surg., 119: 262, 1944.
[8] Wesson, M. B.: Tr. Am. Ass. G-U Surg. 32: 347–358, 1939.

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TUMORS OF THE TESTIS: ANALYSIS OF 80 CASES

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Cancer is a challenge not only to the physician and the surgeon, but also to the scientist. The problem is still shrouded in many mysteries. New theories, as yet immature, may enable us to penetrate the fog. Atomic research has provided a fresh approach to diagnosis and treatment of cancer; it may even lead to unveiling its cause.

Advances in diagnosis and treatment of cancer depend not only on laboratory investigations, but also on clinical corroboration of their applicability and utility. The amount, as well as the diversity, of cancer research under way in this country is so extensive that it is difficult for not only the layman but also the medical man to comprehend.

CLASSIFICATION

The classification of testicular tumors proposed by Moore and Friedman now is widely accepted. Recent embryologic and pathologic observations of testicular tumors as to derivation, character and cellular structure have clarified their origin and behavior, permitting greater specificity in therapy.

ORIGIN

Moore and Friedman compare the formation of testicular tumors to the development of placental and fetal tissue: From the primordial germ cell, after fertilization, there derive the placenta (trophoblastic) and the fetus (somatic); in the case of a testicular tumor, a transition into a seminoma may occur or, through an intermediary stage of embryonal carcinoma, a chorio-epithelioma or teratoma may be formed—but any combination of these phases may materialize.

ANALYSIS OF 80 CASES OF TESTICULAR TUMOR

A series of 80 patients with tumor of the testis is reported here. Data recorded are compared with that in similar series reported by others. These patients were observed at the Wadsworth General Medical and Surgical Hospital in Los Angeles during the period 1946 to 1950 inclusive. A number of additional cases were recorded at this institution during that period but were excluded from the analysis. Several patients, seen by the Tumor Board and given roentgenologic therapy at this unit, had received surgical therapy elsewhere, and the limited clinical, diagnostic and therapeutic data obtained did not lend itself to detailed or critical analysis. Approximately half of the series had been treated surgically and had received some therapy at other hospitals.

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TABLE 1. *Incidence of testicular tumors in series of 80 patients in relation to average expectancy*

	AVERAGE EXPECTANCY (PER CENT)	INCIDENCE IN SERIES (PER CENT)
Seminoma	35	48.75 (includes 5 cases with minor allied types malignancy)
Embryonal carcinoma	19	26.25 (includes 3 cases with allied malignancy)
Teratocarcinoma	35	20.00 (includes 2 cases with chorio-epithelioma)
Teratoma	7	—
Miscellaneous	3	5.00
Interstitial	1	—

TABLE 2. *Incidence classified as to age of patient and type of testicular tumor*

	20 OR LESS	21–30	31–40	41–50	51–60	61–70	71 OR MORE	TYPE TOTAL
Seminoma	1	11	10	8	4			34
Seminoma & embryonal carcinoma		4						4
Seminoma & teratoma		1						1
Embryonal carcinoma		9	6	1	2			18
Embryonal carcinoma & chorio-epithelioma		2	1					3
Teratocarcinoma		8	5	1				14
Teratocarcinoma & chorio-epithelioma		1	1					2
Lymphosarcoma			1					1
Leiomyosarcoma			1					1
Reticulum cell sarcoma						1	1	2
Age Group Total	1	36	25	10	6	1	1	80

Seventy-seven were Caucasian; there was only one Negro in the group. Most were married or had been married. Their average age was 34, slightly lower than in similar series reported by others.

The incidence of seminoma and embryonal carcinoma was higher than the average expectancy, while that of teratocarcinoma was lower; there were no adult teratomas (table 1). Lone chorio-epitheliomas and interstitial cell types of growth were not found. The types of tumor recorded at different age levels are given in table 2. Almost half of the patients were aged 21 to 30; the next most frequent age bracket was 31 to 40. In the patients aged 41 to 60 the majority of tumors were seminomatous. Only 2 patients were older than 60; both had reticulum cell sarcoma. There was a slight preponderance of right-sided neoplasms, 53 per cent. One lymphosarcoma was bilateral.

ETIOLOGY

Trauma. Although trauma was mentioned by 27 per cent of Lewis's patients with testicular tumor, he was of the opinion that trauma probably was not of

TABLE 3. *Previous operations*

	NUMBER PATIENTS	
Herniorrhaphy (total)		5
Ipsilateral (1 patient had three such repairs)	3	
Bilateral	2	
Orchiopexy, ipsilateral		3
Vasoligation, bilateral		1
Total		9

etiologic significance. The possibility that trauma might be an exciting factor prompted us to re-examine the historical data in our series: Seventeen and a half per cent had a history of direct or indirect trauma. The interval between actual injury and initial symptoms averaged 43 months, the shortest being one week, and the longest 11 years. Whether or not previous operative procedures (table 3) might have been a contributing factor from the standpoint of trauma also was considered, but such a relation was not revealed, excluding the traumatic factor incident to orchiopexy.

Cryptorchism. Malignant change in undescended testes was recorded in 11 per cent of 7000 cases reviewed by Gilbert and Hamilton. A history of cryptorchism was determined in 10 of our patients (12.5 per cent). There was unilateral cryptochism with ipsilateral tumor in 8 patients and bilateral cryptorchism with a unilateral tumor in 2 (table 4). Three patients with unilateral masses had undergone orchiopexy. One, in whom orchiopexy had been done 10 years previously, had a mass in the right pelvic region that proved to be seminomatous, although evidence of tumor was not found in the atrophic testis on the right side. This probably exemplifies Friedman's contention that a primary testicular tumor may produce recognizable metastases and then disappear entirely, so that only remnants of scar tissue exist in the testis, the original tumor having completely regressed.

Other factors. The possible significance of orchitis, epididymitis, and other diseases to testicular tumors was investigated, but valid associations could not be deduced. Other malignant lesions were found in only 2 patients (table 5). Familial carcinomatous traits were not revealed in the histories of our patients, and only 1 instance of cryptorchism in a relative was disclosed.

TABLE 4. *Cryptorchism*

	NUMBER PATIENTS	PER CENT TOTAL SERIES
Unilateral cryptorchism with ipsilateral tumor	8	10.0
Bilateral cryptorchism with unilateral tumor (1 patient had spontaneous descent at age 14)	2	2.5
Total	10	12.5

TABLE 5. *Possible predisposing factors*

	NUMBER PATIENTS		
Local inflammatory lesions, total			22
Mumps orchitis (20 patients had history of mumps without orchitis)		5	
Ipsilateral	2		
Contralateral	2		
Bilateral	1		
Epididymitis:		5	
Ipsilateral	3		
Lateralization (?)	2		
Urethritis:		12	
Gonorrheal	10		
Nonspecific	2		
Local noninflammatory lesions, total			5
Hydrocele, ipsilateral	5		
Syphilis			4
Tuberculosis, pulmonary and rectal			2
Malignant lesions:			2
Fibrosarcoma, wrist	1		
Lymphosarcoma, axilla	1		
Total			35

COMPLAINTS

The intervals between onset of symptoms and examination and between symptoms and surgical intervention are given in table 6. The shortest lapse between symptoms and examination was 2 days and the longest 13 years, while the average in 75 patients was almost ten months. The shortest period between onset of symptoms and operation was ten days and the longest thirteen years; the average in 74 patients was eleven and a half months. Such "averages" are not, in themselves, particularly significant, but in 74 patients the individual periods of delay between examination and surgical intervention totalled one hundred and eleven months—or about a month and a half to each case.

Surprisingly, in 16 patients (20 per cent) the initial complaint was not referable to the testis or to the scrotum (table 7). A painful nodule or swelling of the testis

TABLE 6. *Delay in examinations and operations*

Interval between onset of symptoms and examination:		
Shortest period	2 days	
Longest period	13 years	
Average in 75 patients (not known in 5)		9.9 months
Interval between onset of symptoms and operation:		
Shortest period	10 days	
Longest period	13 years	
Average in 74 patients (not known in 6)		11.5 months
Average interval between examination and operation		1.6 months

TABLE 7. *Initial complaints*

	NUMBER PATIENTS	
Localized to scrotum or testis		64
Swelling or nodules, painless	52	
Swelling or nodules, painful	12	
Other complaints		15
Abdominal mass and pain	8	
Fatigue, paresthesia of legs, vomiting	1	
Vomiting, epigastric pain, hemoptysis	1	
Pain, right lower quadrant	1	
Pain, left flank	1	
Pain, right inguinal region	1	
Swelling, left side of neck	1	
Swelling, right side of neck	1	
Not recorded		1
Total		80

was present in 12 (15 per cent). In 8 (10 per cent) there was an abdominal mass.

One patient complained of an abdominal mass of 4 months' duration. Sixteen months previously biopsy of an axillary node had been reported as lymphosarcoma. Apparent regression followed radiation therapy. On admission to this hospital, in addition to the abdominal mass, he was found to have a hard, nodular left testis and roentgenologic evidence of hilar adenopathy. Diagnosis of abdominal lymphosarcoma with metastases to the chest and testis was entered; however, biopsy of the testis was reported as "seminoma." The patient died in a month. All organs and nodes were seats of seminomatous processes, there being no evidence of lymphosarcoma. Nevertheless, review of the initial axillary node biopsy by our pathologists corroborated the original diagnosis of lymphosarcoma.

DIAGNOSIS

Physical examination. Every physician should be aware of certain diagnostic features of testicular tumor, since percentage of cure is as closely related to early diagnosis as to proper treatment.

Physical examination of every patient, whether normal or ill, should include careful inspection of the genitalia. A hard, heavy, nontender, nontransilluminating, unilateral scrotal mass of any size in a young adult is presumptive evidence of a neoplasm, although the older age groups are not exempt. Vague abdominal symptoms, or abdominal or cervical masses in a young man may point to a testicular tumor. Symptoms of obstruction of the upper urinary tract, particularly if unilateral, may stem from a tumor of the testis. The presence of hydrocele in a young male patient should arouse one's suspicions as to possible associated neoplasia. Gray and his co-workers at the Mayo Clinic reported this lesion in 8.7 per cent of their series of tumors of the testis. Seven per cent of our patients had hydrocele.

TABLE 8. *Clinical corroboration of hormonal assays in 80 patients*

	NUMBER TESTS	TESTS CONFIRMED CLINICALLY (PER CENT)
Prolan A	31	75
Friedman or Aschheim-Zondek	36	80
Pregnandiol	23	70
Average clinical corroboration		75

Gynecomastia may be caused by feminizing tumors and chorio-epithelioma. However, of our 7 patients with ipsilateral and bilateral symptoms referable to the breast or nipple, only 2 had associated chorio-epithelioma.

Melicow described the sign of the vas as a helpful differential diagnostic point during the physical examination. When inflammatory lesions are present in the scrotum, the vas becomes considerably thickened and irregular; in neoplasm it tends to remain uninvolved.

When either the cause or the character of a scrotal mass is in doubt, we believe that surgical exploration is mandatory—to determine definitely whether a tumor is present.

Isotopes. Roswit and his colleagues commented on their experience with radioactive phosphorus (P^{32}) in the diagnosis of testicular tumors. Our isotope laboratory group is investigating this method of diagnosis. We are hopeful that other radioactive substances may be used with more success.

Gonadotrophins. All evidence, both experimental and clinical, indicates that chorionic gonadotrophin is elaborated by chorionic tissue and that embryonic tissues *per se* do not produce it; furthermore, no other tissues are known to produce this hormone. Chorionic gonadotrophin, when present in the urine of a patient with a testicular tumor, is identical with that found in the urine of pregnant women. In testicular choriocarcinoma the hormone is produced by the trophoblastic tissue of the tumor.

Our results of hormonal assays are encouraging, as shown in table 8. In nearly equal series of tests on all types of tumors the results proved to be 75 per cent correct, as corroborated by all but postmortem observations. When we added to clinical data the facts secured by detailed postmortem studies in 15 cases, the

TABLE 9. *Postmortem corroboration of hormonal assays and seroflocculation tests in 15 patients*

	NUMBER TESTS	POSTMORTEM CONFIRMATION OF TESTS (PER CENT)
Prolan A	10	80
Friedman or Aschheim-Zondek	10	80
Pregnandiol	9	88
Seroflocculation	10	90
Average postmortem corroboration		84.5

TABLE 10. *Roentgenologic evidence of metastases*

	NUMBER PATIENTS		
Pulmonary			23
Preoperative		5	
Postoperative		11	
Preoperative and postoperative		6	
No operation		1	
Osseous (roentgenograms of spine were negative in 1 case in which metastases found at autopsy)			0
Upper urinary			16
Hydronephrosis		9	
Ipsilateral	7		
Contralateral	1		
Bilateral	1		
Deflection of ureter:			
Ipsilateral	4		
Contralateral	3		
Total			39

TABLE 11. *Diagnoses on admission*

	NUMBER PATIENTS		
Local			60
Testicular tumor		48	
Inflammatory lesions		6	
Acute epididymitis and orchitis	1		
Acute orchitis, nonvenereal	1		
Chronic hypertrophic orchitis	1		
Chronic epididymitis	1		
Tuberculosis of testis (?)	2		
Noninflammatory lesions		6	
Hydrocele	4		
Spermatocele	1		
Inguinal hernia with hydrocele		1	
Abdominal			3
Abdominal tumor, unspecified		1	
Acute appendicitis		1	
Hepatitis		1	
Other			4
Hodgkin's disease or thyroid adenoma		1	
Carcinoma of thyroid		1	
Pyonephrosis, left		1	
Secondary anemia		1	
Not recorded			13
Total			80

TABLE 12. *Extrascrotal masses on admission*

	NUMBER PATIENTS
Supraclavicular (ipsilateral)	2
Abdominal	15
Inguinal (ipsilateral)	1
None	62
Total	80

TABLE 13. *Preoperative diagnoses*

	NUMBER PATIENTS	
Testicular		60
Testicular tumor	53	
Scrotal mass, left	1	
Epididymitis and orchitis	1	
Orchitis, acute, nonvenereal	1	
Tuberculosis, scrotal	1	
Hydrocele	1	
Spermatocele	1	
Torsion of testis	1	
Extratesticular		5
Hodgkin's disease	1	
Metastatic carcinoma, abdomen	1	
Acute appendicitis	1	
Pyonephrosis	1	
Hernia, inguinal, and hydrocele	1	
Not recorded		15
Total		80

percentage of corroboration of the hormonal assays arose to 85 per cent (table 9). Therefore, we are continuing to employ biochemical assays in our study of testicular neoplasms. Hall reported the value of a seroflocculation reaction in cancer. It was positive in 90 per cent of our group of testicular tumors. This test may be a means of diagnosing occult lesions in the testes. We are continuing its use in our present series of patients treated by more radical surgical intervention.

Pyelo-ureterograms disclosed hydronephrosis in 9 cases; 7 ipsilateral, 1 contralateral and 1 bilateral. Deflection of the ureter occurred on the same side in 4 instances and on the opposite side in 3 (table 10).

Roentgenologic bone surveys for metastases were not of diagnostic significance in this series; at postmortem examination 9 instances of bony involvement were

TABLE 14. *Agreement of clinical, operative gross and pathologic diagnoses*

	AGREED	DISAGREED
Clinical and operative gross	41	12
Clinical and pathologic	61	7
Operative gross and pathologic	48	4

TABLE 15. *Method of orchiectomy and where performed*

Method of Orchiectomy:	
High inguinal	33
Low inguinal	6
High scrotal	2
Scrotal (Secondary resection of cord for suspected tumor—not found—done in 2 cases)	32
Abdominal exploration	4
Abdominal	1
Biopsy of testis	1
None	1
Total	80
Where Performed:	
Wadsworth General Medical and Surgical Hospital, Los Angeles	41
Elsewhere	39
Total	80

observed. Surprisingly, in only 48 cases (60 per cent) was "testicular tumor" diagnosed on admission. Furthermore, in 21 cases (26 per cent) the admission diagnosis was not related primarily to the testis (table 11).

Metastases to other organs and tissues may reveal the existence of a tumor of the testis before the local condition is even suspected. In some cases, even after positive biopsy of an extratesticular mass, careful palpation of the genitalia fails to disclose a lesion. If the mass is unilateral, exploration and even partial bivalving of the testis is definitely indicated to establish the diagnosis. In a patient in whom this was not done, autopsy revealed a minute tumor of the testis on the ipsilateral side of a retroperitoneal mass.

Extrascrotal masses (table 12) that eventually were determined to be metastases from the testicular lesion were recorded on admission in 18 patients (22.5 per cent). During physical examination of these men the attention of the examiner may well have been diverted from the local focus of the disease.

Preoperative diagnoses. Testicular tumor was the preoperative diagnosis in only 53 of the 80 cases (66 per cent) (table 13). The urgent necessity for surgical exploration of scrotal masses is thus emphasized. A comparison of clinical, operative gross, and pathologic diagnoses is given in table 14.

TREATMENT

During the last year and a half we have used relatively more extensive surgical therapy for malignant tumors of the testis. In the present communication we evaluate the results of less radical treatment—orchiectomy and radiation—employed during the five-year period 1946 to 1950.

In 39 instances orchiectomy was done through an inguinal incision, the method of choice on our service (table 15). The entire cord, up to the internal ring, was removed; this approach involves minimal handling of the testis until occlusion of the vascular pedicle and lymph channels is accomplished.

TABLE 16. *Roentgenologic therapy*

	AVERAGE INCLUSIVE PERIOD (MONTHS)	AVERAGE TOTAL CUTANEOUS DOSAGE (r)
Seminoma	12.1	11,695+
Seminoma and embryonal carcinoma	13.0	16,811
Seminoma and teratoma	2.0	13,000
Embryonal carcinoma	4.0	11,345+
Teratocarcinoma	5.7	12,329+
Teratocarcinoma and chorio-epithelioma	2.0	10,664
Reticulum cell sarcoma	3.0	4,840
Leiomyosarcoma	3.0	7,140
Lymphosarcoma	24.0	12,200
Average (exclusive of sarcoma)	6.5	12,320

At the time of operation 13 patients had blood vessel or lymphatic extension up the cord; thus, nearly a third of these testes demonstated presumptive evidence of metastases or definite extension. The interval between onset of symptoms and definitive therapy in these 13 cases was approximately one year. In most instances the patient was responsible for the delay; in others the physician had procrastinated. The necessity for careful examination, prompt diagnosis, and rapid execution of treatment in suspicious cases, therefore, cannot be overstressed.

The average inclusive period of radiation therapy, exclusive of sarcoma, was about six and a half months. The total average cutaneous dosage, again exclusive of sarcoma, was approximately 12,000 r. (table 16).

RESULTS

It is possible to evaluate five or ten-year survivals in only a portion of the series, since insufficient time has elapsed in some patients. Complete data will not be available until the end of 1955 when the five-year interval will have elapsed for the last patients in the series.

At the time of preparing this report (April 1953), 48 of the 80 patients were living and 29 had died—a mortality of 36 per cent; 3 patients were definitely lost to follow-up.

Table 17 presents the average survival time of the 48 living patients, classified as to the type of tumor. The average interval since operation is 47.8 months. The longest survivals are in the seminoma group, with 3 ten-year survivals and 9 five-year. The embryonal carcinoma and teratocarcinoma groups each have 2 five-year survivals to their credit.

In table 18 are presented survival periods of the 29 patients who have died. Here again those with seminoma survived longer periods, the longest being 44 months and the average 15 months.

Of significance is the fact that in the living patients the lapse between onset of symptoms and surgical intervention averaged 6 months whereas this period in the group who have died averaged nearly eleven months—a contrast that again points to the urgent need for early diagnosis and prompt treatment.

TABLE 17. *Intervals since operation in patients who are living*

	NUMBER PATIENTS	AVERAGE SURVIVAL
Seminoma	28	7 years, 4 months
Embryonal carcinoma	11	3 years, 5 months
Embryonal carcinoma and Chorioepithelioma	1	2 years, 6 months
Teratocarcinoma	7	3 years, 8 months
Leiomyosarcoma	1	3 years
	48	3 years, 11.8 months

TABLE 18. *Postoperative survival of patients who have died*

	NUMBER PATIENTS	AVERAGE SURVIVAL
Seminoma	6	1 year, 9 months
Embryonal carcinoma	10	11 months
Embryonal carcinoma and Chorioepithelioma	2	8 months
Teratocarcinoma	7	1 year, 1 month
Teratocarcinoma and Chorioepithelioma	1	1 year, 2 months
Reticulum cell sarcoma	2	10 months
Lymphosarcoma	1	2 years
	29	1 year, 3 months

TABLE 19. *Metastases recorded at 19 postmortem examinations*

	NUMBER PATIENTS	NUMBER ORGANS INVOLVED
Seminoma	5	29
Embryonal carcinoma	5	17
Embryonal carcinoma and Chorioepithelioma	3	19
Teratocarcinoma	3	11
Teratocarcinoma and Chorioepithelioma	2	8
Lymphosarcoma	1	7

In 19 of the 29 fatalities postmortem examination was done (table 19). The regional nodes were involved unilaterally in 2 cases and bilaterally in 15. Other organs involved, in order of frequency, were liver, lungs, vertebrae, pancreas, kidney, adrenals, cerebrum and stomach.

It was considered, heretofore, that seminomas metastasize late and that metastases occur in lymph nodes predominantly and in other organs rarely. In this series, however, although in only 5 of the 19 autopsies was a seminoma the primary tumor, the average number of organs involved in metastatic spread from seminoma was greater than was determined in the other testicular tumors. Curiously, seminomatous metastates to the cerebrum or cerebellum were not found, despite the widespread involvement of other anatomic sites. In all other types of teratoid tumors numerous metastases were noted in the contents of the

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BILATERAL CONCOMITANT SEMINOMA

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Concomitant malignant testicular tumors in normally placed testicles are rare. There is not a case in the Tumor Registry of the Army Institute of Pathology at Washington, D. C. Hamilton and Gilbert[1] analyzed 7,000 case records of testicular tumors and found 134 cases in which each testicle was involved in cancer at some time. These cases were not of simultaneous involvement and frequently months and years elapsed between involvement of the remaining testicle after removal of the other, thus not ruling out metastasis. In 1949, Hotchkiss and Laury[2] in reviewing the medical literature to the year 1805 were able to find only 21 cases and reported one of their own. Since this review one additional case[3] has been added which, with the case to be reported, brings the total number of cases to twenty-four. If an analysis of the cases of concomitant involvement of the testicles by malignant tumor is further studied it is found that of the 23 cases reported only twelve fall into the classification of primary testicular malignancy as described by Moore or interstitial cell tumor with the remaining cases being of lymphoid or sarcomatous origin. Of the twelve patients with primary testicular tumors six are of embryonal carcinoma,[4, 5, 6, 7, 8, 9] two of encephaloid tumor,[10, 11] type indiscernible, two of interstitial cell tumor,[3, 12] one of carcinomatous teratoma,[13] and one of adenocarcinoma.[14] The case to be reported brings the total number of bilateral primary testicular tumors in normally placed testicles to thirteen.

This is the first case of bilateral seminoma arising concomitantly in normally placed testicles. The patient is living 32 months following treatment with no evidence of disease, which is unusual. He maintains normal libido in the absence of both testicles. Emphasis should be placed on earlier diagnosis of testicular malignancy by considering any mass adjacent to the testicles malignant until proved otherwise. In this case five physicians examined the patient and not one suspected malignancy.

CASE REPORT

J. C. D., a 40 year old white male railroad conductor, was admitted to the Medical College of Virginia Hospital on July 17, 1950, with a chief complaint of

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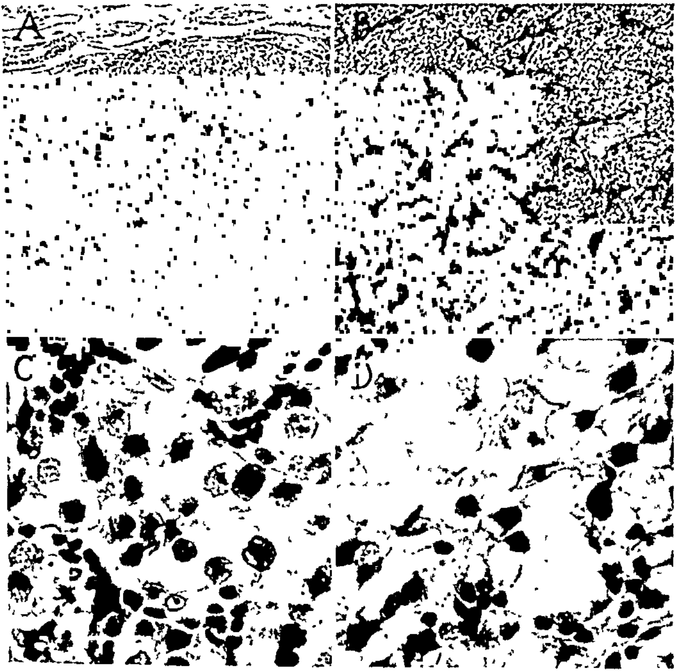

Fig. 1

"swollen testicles" for 6 months. Six months prior to admission the patient was seen by a local physician for swelling of the left testicle and at this time swelling at the base of both testicles was detected with hardness and induration. He gave no history of gonorrhea, stricture, or prostatism and had no urinary symptoms. The patient had had no chills and no fever with no weight loss, and there was nothing in the history to suggest tuberculosis. The patient was given penicillin therapy and sitz baths periodically with no improvement, and because the testicular swelling increased with more hardening but little pain he was admitted to this hospital.

Laboratory examinations revealed nonprotein nitrogen 28, hemoglobin 14, with 4,800,000 red blood cells and a white count of 7,300 with a normal differential. The urine was normal, the Wassermann test negative, and a chest film was within normal limits.

Physical examination revealed a well-developed, well-nourished man lying comfortably in bed not appearing acutely nor chronically ill. The temperature was 98.4, pulse 82, respirations 20, and blood pressure 120/80. The positive physical findings were limited to the genitalia. Both testicles felt normal except in the region of the power pole, which was poorly defined and could not be distinguished from the head of the epididymis which was felt to be thickened on both sides. Both vasa felt normal. The preoperative diagnosis was bilateral chronic epididymitis and the patient scheduled for bilateral epididymectomy.

The testicles were exposed through curved incisions beginning on either side at the external ring and extending down into the scrotum. The testicles revealed a whitish, rounded, firm lesion at either lower pole with fibrosis of the adjacent epididymis. Neither testicle was grossly enlarged. A frozen section was done on each testicle and the diagnosis was seminoma. Following this, bilateral orchiectomy was carried out by ligating each spermatic cord and adjacent structures in turn high in the inguinal canal. The wounds were closed in layers.

Pathological report: Grossly the right testicle measured 4 by 4 by 1½ cm. and the left 3½ by 3½ by 1½ cm. Both testicles at the lower pole adjacent to the epididymis showed a grayish white tumor measuring 1 by 1 by 1½ cm. and displacing the testicular tissue. The epididymides showed some thickening bilaterally.

Microscopic and histological appearance revealed an identical picture in sections of the right and left testes (fig. 1, *A* and *B*). This comprised a tumor made up of polyhydral and rounded cells of uniform arrangement (fig. 1, *C* and *D*). Formations of alveolar configurations separated by collagenous stroma were seen. No acini were evident. There was slight variability in the size of the cells. For the most part, the cell borders were distinct and delineated abundant cytoplasm with clear or faintly granular cytoplasm. In some of the tumor cells the cytoplasm had a reticular appearance. The nuclei were distinctive, being uniform, round or oval, and centrally placed. Tumor giant cell formations were rarely seen. In the typical neoplastic cell the nuclear chromatin filaments or granules were evenly dispersed and varied somewhat in amount from one cell to the other. The majority of the cells contained one prominent nucleolus but two or three such structures were frequent. Pathological or heterotype mitoses were abundant. Practically all of the cells were hyperchromatic.

The stroma in section from both testes was abundant, consisting of dense bands of collagen and reticulum embedded in which were numerous lymphocytes or lymphoid cells. Occasionally lymphoid follicles with germinal centers were obvious. Plasma cells and eosinophilic granulocytes also contributed to the stromal cellular content.

No multinucleated giant cells of the foreign body types were seen. "Epithelioid" cells were absent. The vascularity appeared to be confined to the capillaries running in the connective tissue stromal bands.

The seminiferous tubules adjacent to the tumor mass showed some atrophy. At a distance, however, they were preserved and revealed active spermatogenesis. Atrophic tubules were seen here and there within the tumor. The epididymides appeared free of involvement. Diagnosis: Seminoma of the testes, bilateral (Gordon R. Hennigar, M.D.).

Postoperatively the patient received an average of 2000 roentgens to the lumbosacral area, the aortic nodes, and the mediastinum up to and including cervical seven. This was delivered through multiple ports 10 by 20 cm. in size at a 50 cm. distance using 200 K.V., 20 milliamperes and ½ cm. of copper over a period of 20 days. When last heard from, 32 months following completion of treatment, the patient was living and well with no evidence of tumor and maintaining normal libido.

SUMMARY

The first recorded case of bilateral seminoma is presented which occurred concomitantly in both testicles. Following bilateral orchiectomy and x-ray therapy the patient is living and well 32 months with no evidence of disease and no impairment in potency. The importance of considering all masses in the scrotum, particularly those adjacent to the testicle, as malignant until proved otherwise is emphasized.

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THE USE OF SOLUSPONGE IN PROSTATIC SURGERY

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Even with the advances in the development of new absorbable hemostatic materials the control of bleeding after removal of the prostate is not always wholly successful.

"Solusponge is a physical modification of pure starch, possessing exceptionally high and innate hemostatic properties. These properties are due to the innumerable cell-like spaces which expose a great surface area to the shed blood, and also to the breakdown of sugar products which are released in high concentration on its surface. Such concentrated sugar solutions cause agglutination of red corpuscles and facilitate the clotting action".[1]

The use of Solusponge in Urology was first described by Ritter who carefully studied both the hemostatic and absorptive properties.[2]

The methods of using it and its effect on postoperative care will be discussed. Solusponge comes unsterilized in rectangular strips measuring 2 by 2 by 8 mm. and in two sizes of cones which can be sterilized by autoclaving. Any of the antibiotics or liquid hemostats can be used to impregnate the starch before use.

Our best results were obtained by using one of the following methods. After the prostate has been removed and the arterial bleeding controlled and the prostatic capsule contracted, then the rectangular strips are packed so as to completely fill the prostatic bed. These dry strips are placed in the bed and firmly held in place for one minute with pressure. If a Foley catheter is used the strips are used in a similar manner with one strip on each side around the catheter. The balloon is then blown up and pulled down compressing the sponges in the prostatic cavity. It is held in place by traction on the catheter to the leg for 3 to 4 hours.

A careful study of 75 cases in which Solusponge was used shows in general very few differences as compared with other hemostatic agents.

Two cases had mild secondary hemorrhages controlled by transfusions. The sponge had apparently been ejected into the bladder when the pressure had been relieved.

Two other cases passed small gelatinous pieces of tissue for 8 to 13 days after operation. They were washed out of the bladder by irrigation through a catheter but in no instances were calculi found or was operation for removal necessary. Analysis of these tissues showed no evidence of starch granules and to date no cause has been found for their production.

A comparison with other methods of controlling bleeding shows equally good hemostasis and there is no difference in the number of type of spasms occurring in convalescence. Wound closure is not hastened. Severe postoperative hemorrhage has not occurred in this series.

In summary, Solusponge is a useful hemostatic agent in prostatic surgery. It is easy to handle and is an effective agent in control of bleeding. Its suitability for impregnation with antibiotics may be of value.

180 Fort Washington Ave., New York 32, N. Y.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

[1] Pamphlet describing Solusponge.

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RETROPUBIC PROSTATECTOMY WITH DIVERTICULECTOMY AS A ONE STAGE PROCEDURE

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Diverticulum of the bladder is a reasonably common urological lesion, but has been discussed very little in the recent literature. Senger reported 88 diverticula in 12,000 urological patients, or a ratio of one for every 136 admissions to his clinic. There were thirteen males for every female. Burns states that "diverticulum of the urinary bladder is a complication of clinical importance in about 6 per cent of cases of obstruction at the bladder neck." Because we have combined the operations of diverticulectomy and retropubic prostatectomy as a single procedure, we believe a presentation of our experience is justified.

A diverticulum is a herniation of the bladder mucosa through the muscular wall of the bladder producing a sac which is lined with mucosa and covered with few or no strands of muscle. The usual site of the orifice is in the base of the bladder close to one of the ureteral openings. At this point the bladder musculature is supposedly weakened by the insertion of muscular fibres of the ureteral wall into those of the bladder. Most diverticula are associated with some type of bladder neck obstruction and occur chiefly in males of the prostatic age.

The condition was first reported in 1700 by Bartholin, who found at autopsy a diverticulum of the bladder in a huge scrotal hernia. Morgagni, in 1730 postulated that diverticula of the bladder were caused by bladder neck obstruction which he presumed to be due to enlargement of the prostate.

In 1895 Pean performed the first successful diverticulectomy, and in 1919 Hinman collected 205 cases from the literature, adding 20 of his own. Judd and Scholl, in 1924, reported 87 surgical cases from the Mayo Clinic, with a 7 per cent mortality. They advised the two-stage procedure, doing the diverticulectomy first and establishing bladder drainage, followed by the prostatectomy as a secondary procedure. In 1928 Lowsley and Guiterrez reported some 39 cases, 40 per cent of which were not subjected to operation. The symptoms were usually those of urinary infection associated with bladder neck obstruction. Dees described 95 cases from the Johns Hopkins Hospital in 1940, of whom 78 had demonstrable bladder neck obstruction. He used preliminary suprapubic drainage, even for as long as 40 days. The mortality from diverticulectomy was 10 per cent. The same year Thompson reported 96 patients with the condition from the Mayo Clinic, on whom he had done transurethral resection without attacking the diverticulum. Eighty-eight of them had small prostates, an average of 18 grams of tissue being removed.

Barnes, in 1939, gave his experience with marsupialization of a diverticulum which was so adherent that it could not safely be entirely removed. The technique has been reported more recently by others who have used various cauterizing agents to destroy the mucosal lining of the sac.

Couvelaire, in 1948, reported having done a diverticulectomy and a retropubic prostatectomy as a combined procedure. From a 66 year old man with 420 cc of

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residual urine he removed a prostate weighing 62 gm. The patient made an uneventful recovery with, however, 19 days of postoperative hospitalization.

Diverticulum of the bladder may be suspected in any patient who has a large residual urine, especially a man in the "prostatic age group." The typical patient will have the symptoms of prostatism, usually with an infected residual urine. Occasionally on physical examination the bladder or diverticulum may be sufficiently distended to be palpable suprapubically. The prostate may be a large adenoma, but is frequently of the small fibrous type. Pyuria or hematuria may be found, and bladder stones or tumor may be associated. The diagnosis is made from the history and physical findings, cystoscopy, and cystogram.

Treatment is dictated largely by the severity of the symptoms and findings. Many patients with only a small diverticulum, a minimal residual urine, and mild symptoms may best be treated conservatively by controlling their urinary infection. With a small type of fibrous obstructing prostate and a relatively small diverticulum, a transurethral resection of the gland will relieve the obstruction and allow the diverticulum to drain adequately so that the infection can be easily controlled. If the sac remains large a diverticulectomy is required. In the individual with a large diverticulum, a chronically infected residual urine, and a large prostate, some type of open operation is usually necessary to secure real relief. Often in the past these patients have required prolonged suprapubic drainage to control their infection and make them satisfactory surgical risks. As a rule the diverticulectomy was done at the time the drainage was instituted and the prostatectomy left for the second session.

Diverticulectomy and retropubic prostatectomy as a combined procedure has been recently done by us on three patients without mortality. The results have been most satisfactory and the duration of hospitalization, with its attendant expense, has been materially shortened.

The surgical technique is not particularly complicated, with some variations to meet the individual problem. The patient is placed in a modified Trendelenburg position and the bladder filled sufficiently to distend the diverticulum. The amount of fluid necessary is estimated from the previous study of the residual urine and from the cystogram. A midline suprapubic incision is made, and the bladder and diverticulum exposed. With the diverticulum still distended its dissection from the surrounding tissue is relatively easy until one reaches the region of the neck, which may be deep in the pelvis. At this point it may be necessary to empty the bladder in order to have space in the pelvis to work. Traction is then applied to the diverticulum and the neck and attachment to the bladder are dissected free and exposed. The diverticulum is excised close to the bladder orifice and the bladder mucosa is examined through this opening. A layer of 00 chromic catgut is used to invert the bladder mucosa, and a second layer of 0 chromic to close the muscular defect at the orifice. Hemorrhage is usually very slight if most of the dissection is done with the finger in separating the diverticulum from the surrounding tissue. This procedure is entirely extravesical.

The diverticulum having been removed and the bladder closed, the retropubic prostatectomy is done by the technique described by Millin, Bacon, and others.

We are careful to remove an adequate wedge of tissue from the floor of the bladder neck. After bleeding is controlled a 24F Foley catheter is inserted through the urethra into the bladder and distended with 60 cc of fluid. The incision in the prostatic capsule is then closed with interrupted sutures of No. 0 chromic. The catheter is irrigated to be sure that it is not obstructed and draining freely. Cigarette drains are placed to the region of the neck of the diverticulum and to the retropubic space. The rectus sheath and the skin are closed separately. At least one transfusion is given during the procedure.

Postoperatively all the patients have done well. They are given adequate fluids, sedation, and antibiotics. We are inclined to leave the catheter in place for as long as 12 days. The suprapubic drains are removed on the fourth day if there is no evidence of leakage or infection. On removal of the Foley catheter all the patients have voided freely with good control and no residual urine of consequence. Follow-up cystograms have shown uniformly satisfactory results.

CASE REPORTS

Case 1. A 64 year old man was first seen on June 22, 1951 complaining of hesitancy, straining, small stream, and nocturia, which had been present for over a year. He was a small thin man, and did not appear acutely ill nor uncomfortable. The prostate was graded 2 plus, elastic and adenomatous in texture. He voided slowly and was found to have 350 cc of clear residual urine. Urological study was recommended. He did not return until 6 weeks later when he had a rather severe hematuria of several hours duration. He now had an apparently distended bladder from which a large amount of urine and clots were evacuated. He was sent to the hospital with a Foley catheter in place.

Urograms revealed a normal upper urinary tract, but the cystogram showed two large bladder diverticula which looked like the ears of a caricature in the Sunday comics. Cystoscopy showed coarse bladder trabeculation, moderate intraurethral intrusion of the lateral lobes of the prostate, and a diverticulum opening just lateral to each ureteral orifice. Blood studies were normal, and his internist felt that he was an excellent operative risk.

The operation was done on August 8, 1951. The procedure as outlined was followed except that both diverticula were dissected free before either was opened. The prostatectomy was somewhat difficult because the gland was relatively small and rather adherent. His convalescence was uneventful and he was discharged from the hospital on the fourteenth postoperative day. The pathologist reported nodular hyperplasia of the prostate weighing 24 gm.

Cystograms made on January 2, 1952, some 5 months later, showed that he had no defect in the bladder and excellent emptying. The urine was clear.

Case 2. A 67 year old white man came into the office with a Foley retention catheter in place. He had suffered a complete urinary retention three days before, and "three quarts of urine" had been removed elsewhere. He was an alert intelligent man, and appeared to be quite comfortable. He said that several months previously he had been on a long automobile ride and had retained the urine until he was quite uncomfortable. At this point the car went over a sudden hard bump and he had a very severe pain in his pelvis, followed by relief from his intense desire to void. However, following this episode he had no increase in the symptoms of prostatism from which he had suffered for several years. For a week prior to the present retention the symptoms had been increased and he had been voiding more frequently than usual. There had been no hematuria nor pyuria, and this was his first experience with urinary retention.

Rectal examination showed an enlarged adenomatous prostate which was graded 3 plus. Excretory urograms revealed a medial deviation of the lower right ureter as though it were displaced by some mass in the pelvis. Cystograms showed a large diverticulum on the right side which was obviously pushing the ureter out of its normal alignment. Cystoscopy was done and marked trabeculation of the bladder and a big trilobar hypertrophy of the prostate were found. Near the right ureteral orifice there was the opening of a large diverticulum. The blood count and chemistry were normal, and his physician felt that his general condition was good except for slight myocardial damage.

The combined operation was done a few days later. It was not particularly difficult, though he was a rather obese man. When the lowermost portion of the diverticulum was being dissected the ureter was seen and carefully freed without any damage. The mouth of the diverticulum was closed. The retropubic prostatectomy was easily done, though there was rather more bleeding than usual. He left the hospital on the eleventh postoperative day, voiding a good stream and with excellent control. The pathological report was benign adenomatous hypertrophy of the prostate, and the specimen weighed 61 gm.

Six months later this patient's cystogram showed no diverticulum and there was no residual urine. The urine was grossly clear and the result considered most satisfactory.

Case 3. A 64 year old man was first seen in the hospital some 13 days after the surgical repair of a left inguinal hernia. After his operation he had developed an acute urinary retention and was wearing a Foley catheter. He also had a subsiding left epididymitis which increased his disability. He admitted symptoms of prostatism for the last 3 years, but no previous urinary retention. Rectal examination revealed a rather broad flat adenomatous prostate, graded about 3 plus.

Cystoscopy a week later demonstrated a considerable degree of coarse trabeculation of the bladder, a trilobar intravesical intrusion of the prostate, and the mouth of a diverticulum lateral to the left ureteral orifice. Excretory urograms showed a normal upper urinary tract and the cystogram outlined a large diverticulum on the left side of the bladder. His blood findings and blood chemistry were normal.

The operation was performed a few days later. The diverticulum was easily separated and the opening closed easily. The retropubic prostatectomy presented no unusual problem. His postoperative course was a little prolonged on account of his preceding troubles and also because he was a bachelor living in another city. He remained 30 days in the hospital on this account, though his surgical condition would have permitted his discharge on the sixteenth day. The pathologist reported a benign adenomatous prostate weighing 50 gm.

Follow-up cystogram was made 5 months after the operation and revealed no diverticulum and no residual urine. Since he had a good stream and excellent control we considered the result entirely satisfactory.

SUMMARY

Diverticulum of the bladder must be suspected in any patient with a large residual urine and with symptoms of bladder neck obstruction. If suspected, the diagnosis is easy and definite. Treatment may be nonoperative if the sac is small, the residual slight, the urine clear, and there are no obstructive symptoms. Transurethral resection will relieve many patients with small prostates and small diverticula. Patients with large glands and large sacs are best treated by diverticulectomy and open prostatectomy.

We present our experience with 3 patients upon whom we have combined diverticulectomy and retropubic prostatectomy as a one-stage procedure. There was no mortality, the hospital expense was reduced by the shortened convalescence, and the postoperative results have been most gratifying.

Santa Barbara, Calif.

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RETROPUBIC PROSTATECTOMY: A REVIEW OF 678 PATIENTS

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This is a survey of 678 patients having undergone retropubic prostatectomy during the 6-year period from 1947 to 1953. The discussion will neither set forth the method nor extol the merits of this procedure. However, to provide a more comprehensive perspective of the status of retropubic prostatectomy I have included a comparable number of cases from both the domestic and foreign literature.

In this group of 678 retropubic prostatectomies there is included 171 patients operated upon by the resident staff of the Louisville General Hospital. All other patients were private patients upon whom the surgery was performed by the late Dr. Owsley Grant, Dr. Joseph E. Maurer and the author.

This series of retropubic prostatectomies includes a 22 month period during which other types of prostatectomy were seldom done. Actually this program was stimulated by correspondence between Dr. Owsley Grant and Mr. Terence Millin. Dr. Grant was anxious to substantiate our contention of perineal superiority and at the same time demonstrate the limitations of Mr. Millin's procedure. Following this initial series of retropubic prostatectomies we resumed our previous practice of employing open prostatectomy only in medium to large prostatic adenoma (in excess of an estimated 60 gm.) (fig. 1).

The following topics have been chosen as the basis for our evaluation of retropubic prostatectomy:

1) Postoperative hospital stay (days)

2) Complications: a. Osteitis pubis; b. secondary hemorrhage; c. mortality. There are of course many additional subjects that might be discussed: Vesical neck contractures, necessity of transfusion due to blood loss at the time of surgery, length of catheter period, etc. all are of interest, but the significance of these complications would certainly be reflected indirectly by the topics chosen for comparison. May I say at this point that we have experienced three vesical neck contractures in our series and all in the first 50 patients when we did not understand when and how much of the vesical neck need be resected. In our private patient series the number of transfusions has been less than 12 per cent while in the general hospital series it approaches 90 per cent. This variation is due to our conservative attitude; whereas, in the general hospital the condition of the patients is less good and the popularity of transfusion is evident on all services.

The domestic and foreign series of retropublic prostatectomies for comparison were chosen at random from the literature based only on obtaining a total group size comparable to our series.

In reviewing tables 1, 2 and 3 there is apparent a remarkable similarity (fig. 2). The increased period of postoperative hospitalization in the foreign series is probably not significant since the time of the retention catheter and postoperative complications did not account for a prolonged hospital stay. It would seem that some other factor must be responsible that was not presented.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

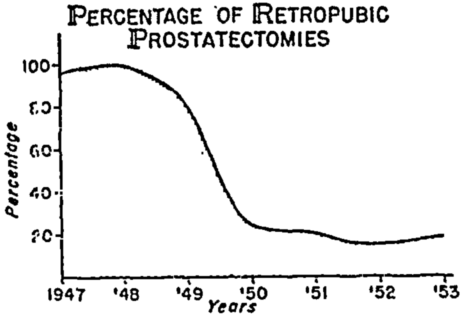

FIG. 1. Percentage of retropubic prostatectomies done annually 1947–1953

TABLE 1. *Domestic series of retropubic prostatectomy*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS PUBIS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Hand and Sullivan............	100	13.5	0.0	0.0	0.0
Bacon........................	102	12.6	0.9	0.9	6.8
Toulson, Mays and Hawkins...	105	14.3	0.0	0.0	4.7
Moore........................	116	10.6	11.2	0.0	1.7
Slotkin......................	119	11.6	0.0		1.6
Scheinman....................	121	11.4	0.0	0.0	0.0
Total........................	663	Average...12.3	2.0	0.9	2.4

TABLE 2. *Foreign series of retropubic prostatectomy*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS DAYS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Ostenfeld....................	114	23	4.3	6.1	5.0
Hickey.......................	50		2.0		2.0
Jacobs.......................	500	16	0.6	0.2	6.0
Total........................	664	Average...19.5	2.4	3.1	4.3

Osteitis pubis is unquestionably the most disquieting factor in retropubic prostatectomy. It is disturbing because of the variable incidence reported (ranging from 0 to 17 per cent). In discussing this complication with authors who have found it most troublesome, we find no apparent difference in technique and often the author reporting the greatest difficulty seemingly exerts great effort in its prevention. Antibiotics are not a factor for we have done many in which neither antibiotics nor any of the sulfonamides were used. Infections in the space of Retzius are not necessarily significant and we have not found any correlation (fig. 3).

TABLE 3. *Present reported series of retropubic prostatectomies*

AUTHORS	NUMBER CASES	POSTOPERATIVE HOSPITAL DAYS	PERCENTAGE OSTEITIS PUBIS	PERCENTAGE SECONDARY HEMORRHAGE	PERCENTAGE MORTALITY
Total........................	678	Average...12.1	0.7	1.3	1.6

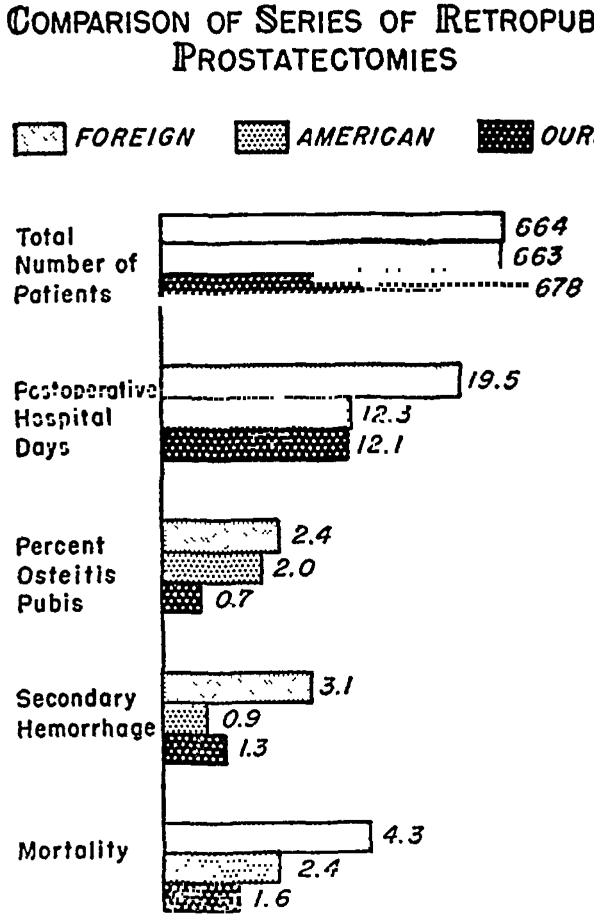

FIG. 2. Comparison of reported series with comparable group of American and foreign authors.

In fact, in only one of our 5 patients with osteitis pubis was there any appreciable visible wound infection. Our incidence of wound infection, of sufficient intensity to warrant additional hospitalization, was found to be 5.3 per cent or a total of 36 wounds. The incidence of osteitis pubis was 0.7 per cent or a total of 5 patients. One of the 5 patients with osteitis pubis occurred in the General Hospital series of 171 patients. Only two patients suffered severe and prolonged symptoms. Millin in reporting 1100 cases of retropublic prostatectomy mentions 9 instances of osteitis pubis; an incidence of 0.8 per cent.

We have used secondary hemorrhage to connote postoperative hemorrhage that has occurred after the initial operative bleeding has subsided. In reviewing

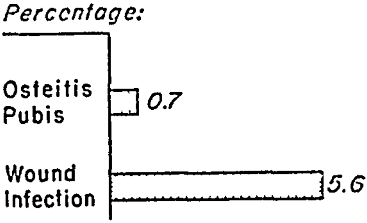

Fig. 3. Relationship between osteitis pubis and retropubic wound infection

the literature it is difficult to judge the definition of secondary hemorrhage as used by some authors. For example, secondary hemorrhage occurring after the catheter has been removed and controlled by re-insertion of a catheter has not been considered in our series to be significant provided that it did not prolong the patient's postoperative course. The criterion used in our series was hemorrhage that necessitated some type of operative intervention. In the group reported it was controlled in all but two of the 9 patients suffering this complication by transurethral fulguration of the bleeding vessel. In two instances the bleeding point could not be localized transurethrally and the operative wound was reopened and the prostatic bed packed which controlled the bleeding immediately. In one instance the bleeding was coming from a large vein in the cut edge of the prostatic capsule anteriorly and in all other patients the bleeding was due to a prostatic artery. Because of these experiences all vessels in the capsular wound edge are securely ligated with a figure of eight suture as are the prostatic arteries. This single variation from Mr. Millin's original technique has put an end to our problem of secondary hemorrhage. We employ fulguration for small oozing points, but never for active arterial bleeding.

In this group of 678 patients there were 11 deaths or an incidence of 1.6 per cent. Except one, all deaths occurred within 14 days following surgery. The one exception was a patient of 73 years who died suddenly 27 days following surgery after he had ridden home, a distance of 58 miles, on his eighth postoperative day. One patient, 56 years of age, died on the fifth day after surgery with an acute coronary thrombosis; another, 78 years of age, had an uncontrollable cardiac decompensation and bronchopneumonia and died in cardiac failure on the thir-

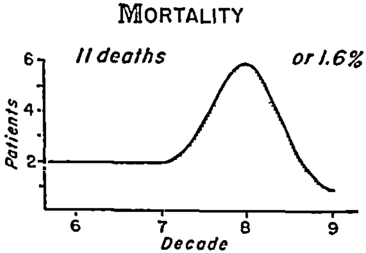

Fig. 4. Comparison of mortality to patient's age

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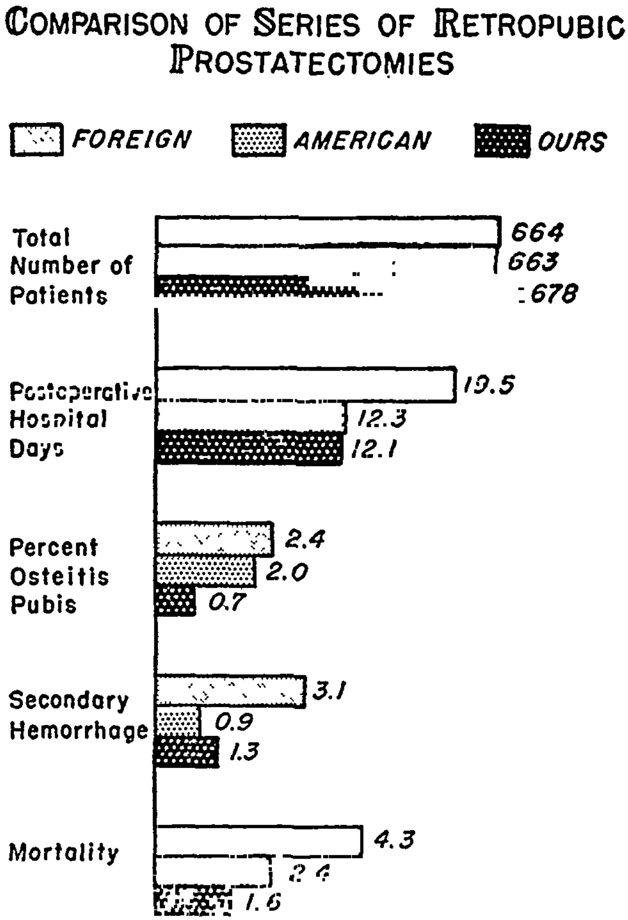

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We have used secondary hemorrhage to connote postoperative hemorrhage that has occurred after the initial operative bleeding has subsided. In reviewing

TABLE 3 *Operative mortality*

TYPE OF OPERATION	NO	MORTALITY RATE
Transurethral	310	2 5%
One stage S P	196	2 2%
Retropubic	12	0 0%
Perineal	12	0 0%

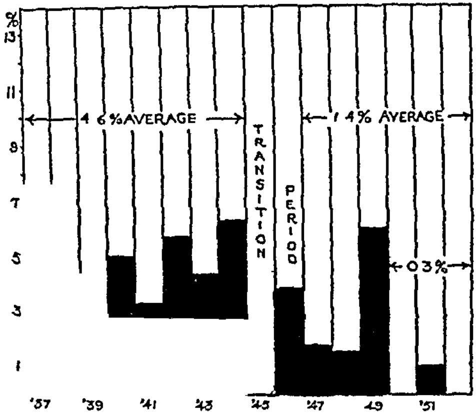

FIG 2 Annual preoperative mortality in public ward patients, Montreal General Hospital

TABLE 4 *Causes of preoperative death*

	1937–1944 8 years	1947 1952 6 years
No of patients	544	539
Pyelonephritis	9	1
Cardiovascular	8	6
P-	3	0
F	2	0
Uremia	0	2
Other causes	2	0
	24	9

Another important change has been the diminution in the incidence of pulmonary embolism In the first group of patients 7 fatal emboli occurred, in the second group only one This further improvement has eliminated an additional 15 per cent of the former deaths The one remaining significant cause of mortality has been disease of the cardiovascular system, but even its incidence has been reduced by half It is not likely that the danger of cerebral hemorrhage or thrombosis or coronary infarction can be removed entirely in this older group of patients

All four, standard, prostatic operations were utilized in the treatment of the more recent group of 530 patients. Most of them, 506 in all, were operated upon by either the transurethral or the one-stage, suprapubic, transvesical procedure. This latter group affords an excellent opportunity for comparing the results of these two operations on the same urological service (table 3). The mortality rate for the two procedures was virtually the same, 2.5 per cent for the one-stage in 196 patients, and 2.2 per cent for the per-urethral in 310 patients. This similarity in mortality rates was somewhat surprising, because an impression had been formed from watching the two groups of patients on the same wards that the mortality in the suprapubic group would be considerably higher. Certainly the suprapubic procedure seems to be a more disturbing operation for the patient, and this fact is borne out by the incidence of immediate postoperative complications, which has been 18 per cent in the one group and 8.3 per cent in the other.

All these changes in operative results are interesting and significant, but the greatest of all seems to be taking place in the reduction of preoperative mortality. In the years 1937 to 1944 there were 24 preoperative deaths with a mortality rate of 4.4 per cent. This is in sharp contrast with the 9 deaths and mortality rate of 1.4 per cent in the period from 1947 to 1952. It would seem that the preoperative fatality rate is still falling for in the past 3 years there has been but a single death, a rate of 0.3 per cent for this three year period. See figure 2.

In the preoperative phase of treatment pyelonephritis again was found to be the commonest cause of death (table 4). It accounted for 9 of the 24 preoperative fatalities in the first group of patients, but was responsible for only 1 in the second group. The incidence of preoperative deaths due to cardiovascular disease in the two groups has remained virtually the same. This may indicate that there has not been a very great change in the general level of health. Deaths from all other preoperative causes have diminished.

The most striking information that has emerged from this study is the startling decrease in deaths due to urinary tract sepsis. It is not likely that this change can be attributed solely to the introduction of antibiotics. Many factors such as less preoperative urethral instrumentation, and greater attention to asepsis have undoubtedly played their part. The change-over from two-stage suprapubic prostatectomy may have had some effect on the mortality rate but under modern conditions the two-stage operation could be performed perhaps with equally good results.

In summary it can be said that the former chief causes of preoperative and operative fatality in prostatic patients virtually have been removed. Further improvement in mortality rates will depend probably on greater attention to the minutiae of treatment and in particular to extreme precautions against cardiovascular accidents.

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IMPORTANCE OF FROZEN SECTIONS IN EVALUATING PROSTATIC NODULES

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It has been axiomatic that precise diagnosis is a prerequisite of rational therapeusis. Many ingenious techniques have been devised for histologic study of palpable nodules in the prostate but only perineal exposure of the gland affords direct access to the entire troublesome posterior lamella. Biopsy via this route, therefore, should have the greatest potential for indicating unequivocally the bona fide candidates for so called radical operations.

The combination of frozen-section examination and simultaneous prostatectomy of appropriate type has no parallel in other diagnostic or therapeutic schemes. This theoretically ideal one stage procedure has attained only limited popularity, however, owing to the exacting technical details of perineal dissection or to skepticism regarding the diagnostic value of frozen sections.

Our study was undertaken in the hope of answering two pertinent questions: 1) Can carcinoma of the prostate, especially early lesions, be diagnosed with consistent accuracy from frozen sections alone and 2) is histologic confirmation of clinical impressions necessarily important when selecting patients for radical prostatectomy?

The survey has been limited to palpable nodules within the prostate of individuals whom we considered suitable candidates for the radical operation. This assured inclusion of those lesions which are usually most confusing to pathologists as well as urologists.

Each prostate was exposed perineally and a generous sample was taken from the indurated portion. In some instances the entire lesion was excised. Multiple biopsy specimens were examined when the induration was less impressive after the gland had been exposed and when the first piece of tissue was reported benign.

PREPARATION OF FROZEN SECTIONS

The frozen sections were prepared according to a standard technique, as follows: The fresh piece of tissue is placed on the stage of a Spencer freezing microtome and frozen with carbon dioxide. Sections are cut with an average thickness of 10 to 15 microns. One of these is floated on the surface of cold tap water and then transferred on a glass rod to Terry's polychrome methylene blue stain for a few seconds. The section is washed in fresh tap water and mounted on a glass slide with a cover slip over it. The mounting medium is tap water.

Sections prepared in this manner will deteriorate because the fluid evaporates and the stain fades on exposure to light. Usefulness of the preparation can be prolonged by sealing the edges of the cover slip with lacquer to prevent evapora-

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tion of the water. Most sections, however, can be preserved for only a little more than twenty-four hours.

It is especially important that the sections be fairly thin and well stained, and some experience with the technique of making fresh frozen sections is required. We routinely have residents in pathology and residents from the various surgical specialties cut our fresh frozen sections and find that after one to three weeks of experience, they make reasonably good fresh frozen preparations. A very essential part of the technique is the use of a sharp knife. Our knives are sharpened after a day's use during which they cut 40 to 50 preparations.

INTERPRETATION OF FROZEN SECTIONS

The interpretation of preparations is made by means of low power and high power microscopy.

The carcinomas of the prostate which give the pathologist difficulty in diagnosis are those which produce well-formed acini. When the acinus 1) loses its papillary projection and 2) becomes smaller and when 3) the cytoplasm of the cell takes up fat and is therefore clear, one should suspect carcinomatous changes. It is not sufficient that only two of these criteria be fulfilled. We have found it necessary for all three to be met in order to make a foolproof diagnosis of carcinoma (fig. 1).

Another very helpful feature to look for in fresh frozen sections, as well as fixed sections, is the presence of collars of tumor cells around nerves. Because the piece of tissue under discussion is usually removed from the posterior lamella of the prostate, nerves and vessels are very readily demonstrated.

In order to become expert in the diagnosis of carcinoma of the prostate from fresh frozen sections, one must be familiar not only with the appearance of numerous carcinomas of the prostate in fresh frozen sections but also with the

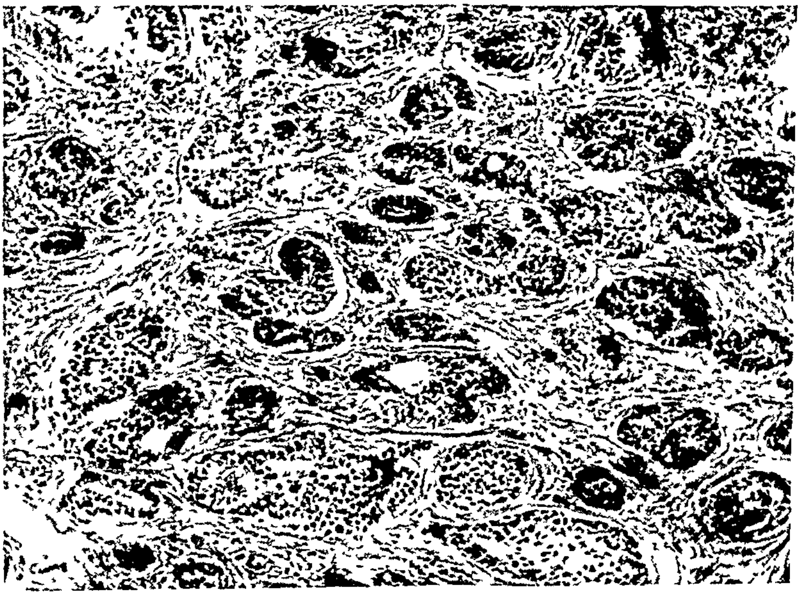

FIG 1. Adenocarcinoma of prostate. Note small lumina, lack of papillary infoldings and cells with clear cytoplasm (fresh frozen section stained with Terry's polychrome methylene blue; ×95).

appearance of benign conditions which mimic carcinoma, such as metaplasia of prostatic epithelium The pathologist who examines questionable lesions of the breast and little else by the fresh frozen technique is probably inadequately prepared to interpret prostatic lesions by this method

ACCURACY OF METHOD

The foregoing morphologic criteria were used to interpret frozen prostatic sections from 45 patients In 40 cases the diagnosis was carcinoma while in 5 instances a benign condition was reported

Each piece of tissue used for frozen section was examined later by means of conventional fixed sections *The original diagnosis was confirmed in every case* Finer details of the permanent sections merely permitted more precise differentiation between grades of malignancy Twelve patients had grade 1 lesions, 26 had grade 2 lesions, and 2 had grade 3 lesions

Admittedly, this is a small series but consistency of this degree has not been unique All our surgical specimens are examined routinely by both frozen and fixed techniques, and the final diagnosis rarely differs from the provisional one

IMPORTANCE OF METHOD

More important than any vindication of the frozen-section technique as a dependable diagnostic procedure is the question of whether or not such studies have significant clinical value, and this we attempted to determine in our study

The 40 patients with positive biopsy specimens were treated by radical perineal prostatectomy All are now impotent, even though 21 are less than 60 years of age, 1 is only 45, and the average age for the entire group is 59 5 years

Four of the 5 patients with benign lesions had no urinary difficulty and the remainder of the prostate was not disturbed The fifth patient underwent simple enucleation of adenomas because of obstructive symptoms The ages of these 5 individuals varied from 41 to 64 years with an average of 55 4 years None has noted any change in his libido or potentia since the operation

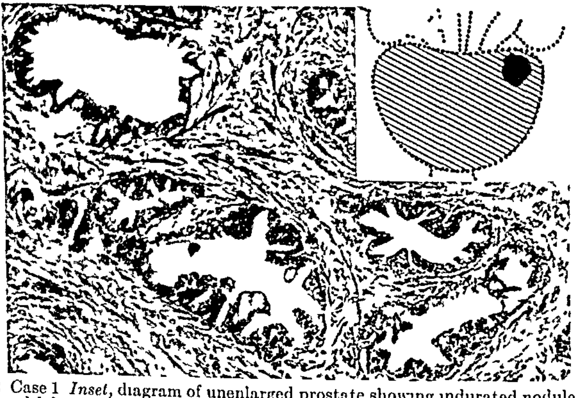

Fig 2 Case 1 *Inset,* diagram of unenlarged prostate showing indurated nodule at base of right lateral lobe Photomicrograph of biopsy specimen taken from nodule shows benign hyperplasia (hematoxylin and eosin, ×65)

It is obvious, therefore, that sacrifice of the entire prostate entails a definite physiologic price which may not be too great for possible "cure" of a potentially lethal disease but one which the unafflicted surgical victim may not accept too philosophically, especially when appropriate preliminary measures could have circumvented this stigma. To date we have found it difficult to be reconciled to prophylactic total prostatectomy.

On the other hand, more serious errors may be perpetrated when patients are denied radical prostatectomy merely because biopsies have not been employed to maximal advantage. Even in retrospect we were unable to discern any special clinical features whereby patients might have been selected for operation more discriminantly. Without adequate biopsies there would have been inevitable errors of omission as well as of commission. Included in our series of 45 cases were several striking examples of potential pitfalls in the simple palpation of prostates.

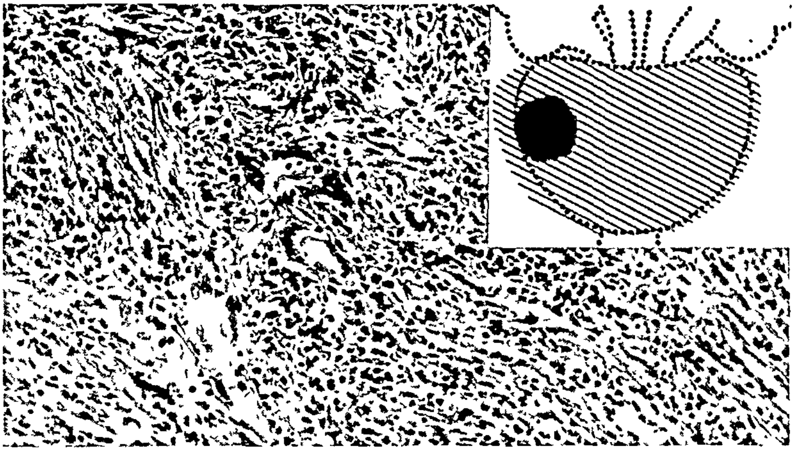

FIG. 3. Case 2. *Inset*, diagram of prostate showing slightly enlarged left lobe which contains a palpable nodule. Photomicrograph of biopsy specimen taken from nodule shows granulomatous prostatitis. Note giant cells (hematoxylin and eosin; ×160).

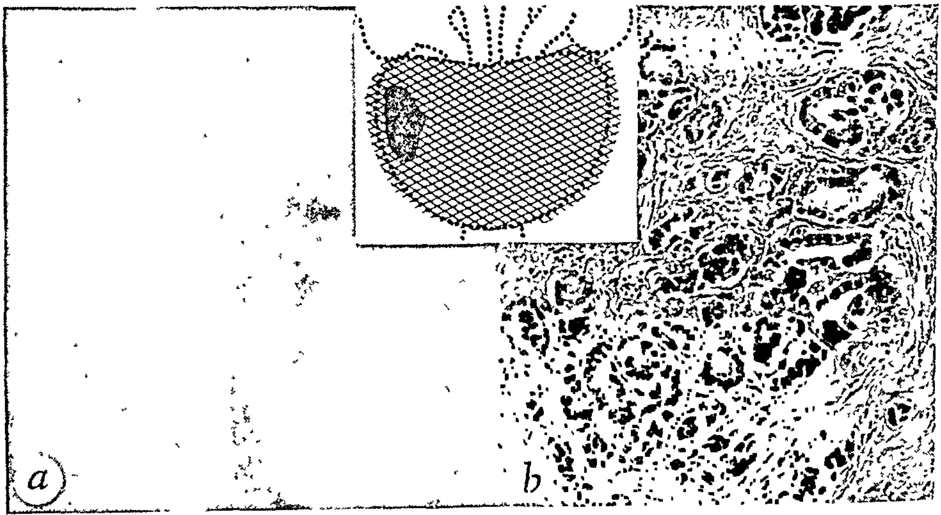

FIG. 4. Case 3. *Inset*, diagram of diffusely indurated prostate with a hard nodule near the left lateral border. *a*, Plain roentgenogram showing multiple prostatic calculi. *b*, Photomicrograph of biopsy specimen taken from nodule showing adenocarcinoma (hematoxylin and eosin; ×135).

ILLUSTRATIVE CASES

Cases 1 and 2, to follow, were thought to be classic examples of early prostatic malignancy.

Case 1. A patient, aged 41 years, had been treated successfully for lymphosarcoma of the neck and had a stony-hard nodule near the base of the right lateral lobe of an otherwise normal prostate. Biopsy showed benign hyperplasia (fig. 2).

Case 2. A patient, aged 57, had an area of third degree induration in the slightly enlarged left lateral lobe of the prostate. Frozen-section examination revealed a localized area of granulomatous prostatitis (fig. 3).

In the other 3 instances of benign disease the condition proved to be either benign hyperplasia or granulomatous prostatitis despite multiple biopsies.

The hazards of hasty interpretation are illustrated by case 3.

Case 3. A 57-year-old patient with diffuse induration in the prostate had been

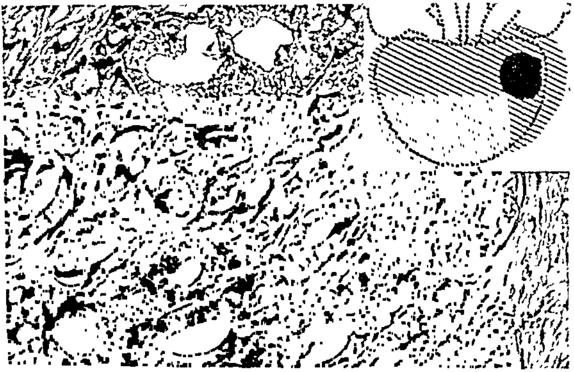

Fig. 5. Case 4. *Inset*, diagram of prostate showing palpable nodule on right. Photomicrograph of biopsy specimen taken from nodule shows adenocarcinoma (hematoxylin and eosin; ×160).

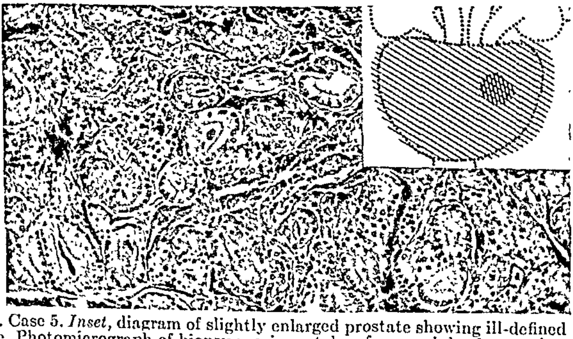

Fig. 6. Case 5. *Inset*, diagram of slightly enlarged prostate showing ill-defined nodule on right side. Photomicrograph of biopsy specimen taken from nodule shows adenocarcinoma (hematoxylin and eosin; ×110).

found to have prostatic calculi, and no treatment had been advised. One area on the left was much firmer than the remainder of the gland. Frozen-section examination disclosed adenocarcinoma (fig. 4).

The importance of continued observation is demonstrated by case 4.

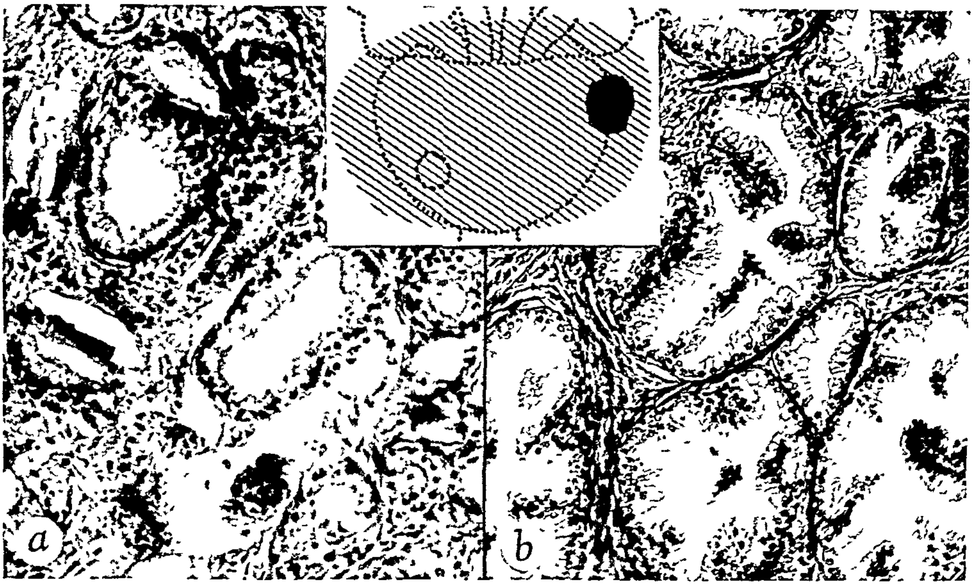

FIG. 7. Case 6. *Inset*, diagram of diffusely enlarged prostate showing markedly indurated nodule on right and site of random biopsy on left. *a*, Photomicrograph of biopsy specimen taken from nonindurated left side showing adenocarcinoma (hematoxylin and eosin; ×150). *b*, Photomicrograph of biopsy specimen taken from indurated portion showing benign hyperplasia (hematoxylin and eosin; ×115).

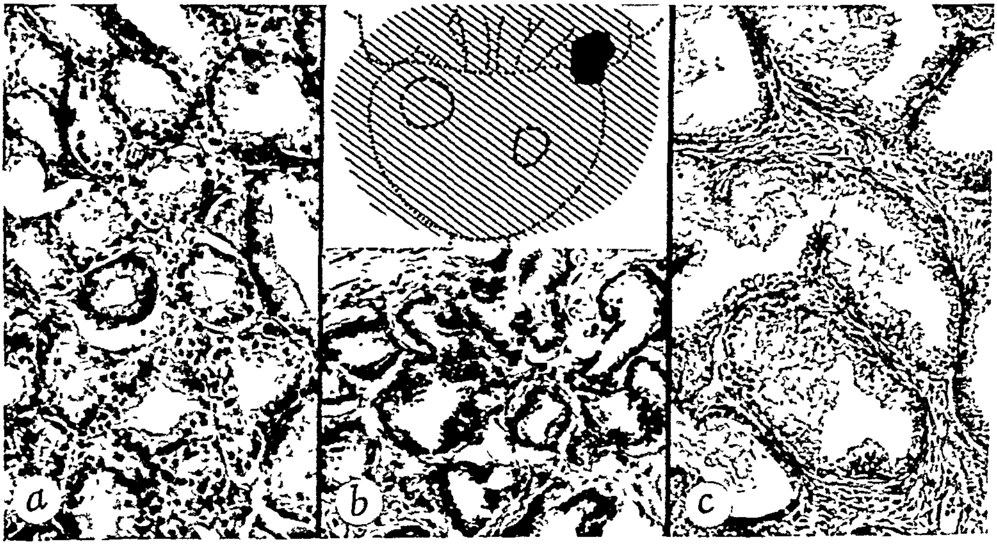

FIG. 8. Case 7. *Inset*, diagram of enlarged prostate showing hard nodule near base of right lobe, and sites of biopsy of left lateral lobe and right side of posterior lamella. *a*, Photomicrograph of biopsy specimen taken from center of enucleated left lateral lobe showing carcinoma (hematoxylin and eosin; ×150). *b*, Photomicrograph of biopsy specimen taken from right side of posterior lamella showing adenocarcinoma (hematoxylin and eosin; ×150). *c*, Photomicrograph of biopsy specimen taken from palpable nodule showing benign hyperplasia (hematoxylin and eosin; ×100).

Case 4 A patient, aged 63, had a smooth, movable nodule in the right lateral lobe which was examined annually for eleven years Between the 1951 and 1952 examinations it became larger and firmer Frozen-section examination disclosed adenocarcinoma (fig 5)

Case 5 offers irrefutable proof that the degree of induration can be a fallacious index and that more prostates should be subjected to biopsy

Case 5 A rather ill defined nodule, only slightly firmer than the remainder of the gland, was noted in a patient aged 63 Most examiners interpreted it as a small adenoma Frozen section examination showed adenocarcinoma (fig 6) Four similar doubtful lesions proved to be adenocarcinomas

The elusiveness of prostatic cancer and the importance of multiple biopsies are demonstrated by cases 6 and 7

Case 6 A patient, aged 69, had prostatic enlargement and typical obstructive symptoms The right lobe contained an extremely hard nodule Frozen section examination disclosed only benign hyperplasia A similar but random biopsy of the unsuspected left side of the gland revealed adenocarcinoma (fig 7)

Case 7 A patient, 70 years of age, had severe obstructive symptoms At the base of the right lobe of the prostate there was a very firm nodule Frozen-section examination showed benign hyperplasia The enlarged lateral lobes were enucleated Routine frozen section examination of the specimen revealed an unsuspected carcinoma within the tissue from the left lobe The remainder of the prostate was removed and a second area of adenocarcinoma was found in the posterior lamella (fig 8) Perhaps multicentric growths of this type account for some of the conflicting opinions regarding the behavior of so called occult lesions

SUMMARY AND CONCLUSIONS

In 45 cases no discrepancies were encountered between diagnoses based on frozen sections obtained by direct perineal biopsy and those made after study of permanent sections from the same tissues If frozen-section biopsy had not been performed, 5 patients would have lost their entire prostates needlessly and would have been destined to be impotent, while 5 other patients with true carcinomas probably would have had no operation If multiple biopsy specimens had not been examined, 2 additional patients would have been left with carcinoma after simple enucleation The results of this study, therefore, seem to warrant the following conclusions

Carcinoma of the prostate can be diagnosed with consistent accuracy from frozen sections, providing the biopsy is adequate Difficulties with the method are probably due to inexperience

To initiate or deny irreversible, definitive therapy solely because of impressions derived from the palpation of the prostate is fraught with considerable hazard Not all nodules of third degree induration are malignant and many carcinomas are only slightly indurated Histologic confirmation of clinical diagnoses is imperative if radical prostatectomy is to be employed judiciously

The combination of direct frozen section biopsy and simultaneous radical perineal prostatectomy, when indicated, still seems to be the logical treatment for early carcinoma of the prostate

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METHODS OF DIAGNOSIS OF CARCINOMA OF THE PROSTATE: A COMPARISON OF CLINICAL IMPRESSION, PROSTATIC SMEAR, NEEDLE BIOPSY, OPEN PERINEAL BIOPSY AND TRANSURETHRAL BIOPSY

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Carcinoma of the prostate is a disease which produces no symptoms in its early stages, yet it kills thousands of patients every year because early diagnosis and appropriate total excision are rare. The detection of early carcinoma depends upon frequent intelligent palpation of the prostate in men over forty plus a high index of suspicion of any induration and biopsy of equivocal areas.[1, 2]

This study was undertaken to evaluate the diagnostic accuracy of digital rectal examination, prostatic smear, and needle biopsy in 99 cases representing various stages of suspected carcinoma of the prostate. In all patients the diagnosis was confirmed by open perineal biopsy, or after transurethral resection in advanced cases. The study shows that needle biopsy properly performed under local anesthesia is a practical and extremely useful technique of diagnosis.

The consensus has been that rectal examination by an experienced clinician is the best diagnostic tool short of open surgical biopsy. Our inquiry emphasizes the importance of this practice.

The important work of Papanicolaou and Traut[3] in diagnosing carcinoma from the examination of exfoliated cells gave hope that this would provide a simple means of detecting early prostatic malignancy. Although many investigators were originally enthusiastic, the majority of them now feel that the method is unsatisfactory in disclosing early carcinoma.[4, 5, 6] However, in late, untreated cases and in experienced hands, it is generally agreed that there is an 80 to 90 per cent positive correlation between the smear findings and the pathological diagnosis.[7, 8]

Although punch biopsy of the prostate has been practised for many years,[9, 10]

Note by editor. The Joseph F. McCarthy prize essay.

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* Pathologist, Culver City Hospital, Culver City, Calif. (Dr. Rosenthal was responsible for interpreting the prostatic smears in this study. The routine pathology was performed by the Department of Pathology, Veterans Administration Center, Los Angeles, Calif.)

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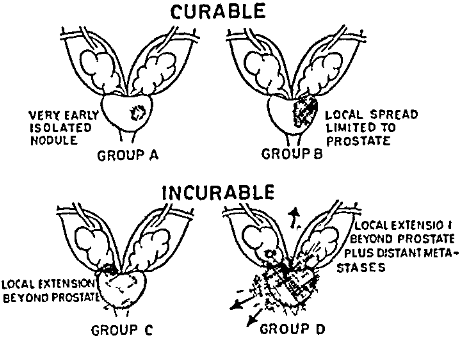
CURABLE
VERY EARLY ISOLATED NODULE
GROUP A
LOCAL SPREAD LIMITED TO PROSTATE
GROUP B
INCURABLE
LOCAL EXTENSION BEYOND PROSTATE
GROUP C
LOCAL EXTENSION BEYOND PROSTATE PLUS DISTANT METASTASES
GROUP D

FIG 1 Classification of cancer of the prostate

it has never become popular There are several reports which show a degree of accuracy for this method which approaches 95 per cent in cases where the clinical diagnosis is reasonably certain[11, 12, 13] Still, most urologists feel that it is inadequate for anything but occasional confirmation of large lesions[14, 15]

This study appraises these diagnostic methods using tissue obtained from open perineal biopsy or transurethral resection to establish their validity

METHODS

We have adopted a clinical classification of prostatic cancer shown in figure 1 Groups A and B represent disease still confined to the prostate and hence potentially curable by proper surgery Groups C and D represent advanced carcinoma, considered incurable by present methods

1) Clinical evaluation Interpretation of prostatic palpation is difficult to standardize We have graded the consistency of the prostate on the basis of 1 to 3 degrees, with 1° representing normal prostatic consistency, 2° indicating definite increased firmness often exemplified by fibrosis or isolated fibroadenomata, and 3° characterizing the stony hardness of prostatic carcinoma or calculi The subtle shadings between these categories are familiar to most clinicians Fixation of the prostate, obliteration of sulci, irregularity of contour of the gland and lateral ligament induration are criteria which, while subjective, are extremely important in determining the status of the neoplasm

For purposes of uniformity one of us examined and graphically recorded his impressions of digital rectal findings in all cases A pictorial record, no matter how individualized, is useful in the evaluation and subsequent re-evaluation of these patients Biopsies were performed whenever there was any question as to the nature of the prostatic induration Clinical impressions of palpatory findings

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[11] Rinker J R and Shuman, W G J Urol , **67**: 709-712, 1952

[12] Semple, J E Brit M J , **1** 1236-1238, 1951

[13] Peirson, E L and Nickerson, D A New Eng J Med , **128** 675-678, 1943

[14] Creevy, C D J A M A , **138** 412-414, 1948

[15] Smith G G J Urol , **64** 671-680, 1950

were classified as 1) carcinoma, 2) probable Carcinoma, 3) improbable Carcinoma. For purposes of conciseness Carcinoma and Probable Carcinoma are subsequently referred to as "Positive" and Improbable Carcinoma as "Negative" clinical impressions.

Cystoscopic findings and results of marrow aspiration, blood chemistries, and X-ray examinations are not included in the present data except as their implications helped to determine group D carcinoma when it was not otherwise suspected.

2) Prostatic smear. In 70 of 99 cases, exfoliated prostatic cells were examined. Expressed prostatic secretion was used in most instances. In some cases when massage was unproductive, the urine sediment after massage was examined. This is in accord with the belief that prostatic fluid is more likely to show diagnostic cells than urine sediment.[4] The Papanicolaou technique of fixation and staining was used.[3] Specimens for this type of examination were obtained in only 70 per cent of the total series. Indwelling catheters, unproductive massage, and occasional tenderness of the prostate were factors interfering wth smear examination in the other 30 per cent of cases.

Approximately 15 per cent of the smears were considered unsatisfactory because of the sparsity of cells. In 25 per cent the numbers of cells were meager and required prolonged scanning of the slides. This is attributed in some cases to an insufficient amount of prostatic fluid or to dearth of exfoliated cells. In other instances, it was apparent that many cells had been lost in the process of fixation and staining. Recently we have attempted to concentrate cells by digestion of the prostatic substrate followed by centrifugation of the freed cells in a tenacious mucus plug which is then smeared and fixed.[16] Our experience has been too limited to offer an opinion regarding the usefulness of this more complicated method. We are, however, encouraged to continue its use (fig. 2, *A*).

The literature is replete with references to the interpretation of exfoliated cytology and its discussion is superfluous here. Standard diagnostic criteria have been used; groups of cells of large size with nucleocytoplasmic disproportion and with variation in nuclear size, shape, and staining density (fig. 2, *B* and *C*). Caution must be used in interpreting seminal vesicle smears which may present cell atypism suggesting carcinoma to the neophyte.[8] In our series only a few patients had received previous hormonal therapy for carcinoma of the prostate, but it is in these cases that the cellular pattern may be distinctly altered with the finding of large squamous and vacuolated cells (fig. 2, *D*).[17, 18]

3) Needle biopsy. The Silverman biopsy needle was used almost exclusively in this series. We have had limited experience with some of the other instruments devised for this purpose (fig. 3, *A*).[19, 20] All have some shortcomings, and sufficient experience with one instrument seems to be prerequisite for obtaining specimens

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[16] Rosenthal, M. and Traut, H. F.: Cancer, **4:** 147–149, 1951.

[17] Peters, H. and Benjamin, J. A.: Surg., Gynec., & Obst., **91:** 660–668, 1950.

[18] Rezek, P. R., Coplan, M. M., Woods, F. M. and Melvin, P. D.: J. Urol., **66:** 379–389, 1951.

[19] Melick, W. F.: J. Urol., **66:** 408–411, 1951.

[20] Veenema, R. J.: J. Urol., **69:** 320–322, 1953.

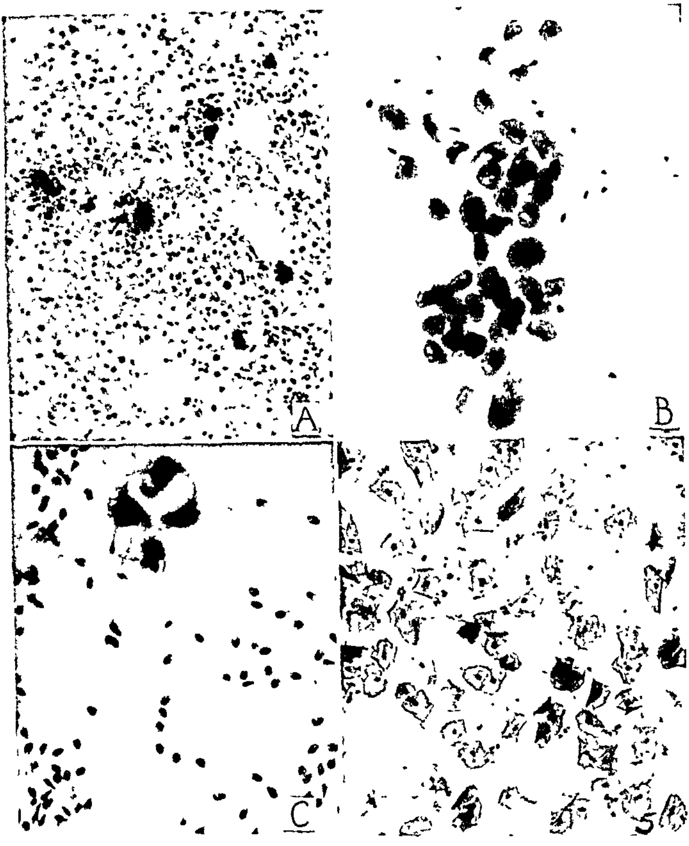

FIG. 2. *A*, concentrated prostatic smear showing several clusters of malignant cells in a single field (×150). *B*, group of prostatic carcinoma cells showing increased nucleocytoplasmic ratio and irregularity of nuclear size, shape, and staining density (×650). *C*, malignant cells arranged in aciniform pattern Small cells are spermatozoa (×650). *D*, concentrated prostatic smear showing large squamous cells Patient had been treated previously with estrogens (×350).

with any degree of regularity. Advantages of the Silverman needle are: It causes minimal trauma, and biopsy may easily be performed under local anesthesia as an office procedure; it is simply constructed; it is easily maneuverable and allows sensitive control with the rectal finger; it is efficient in obtaining adequate tissue once the technique is mastered. The chief disadvantage when compared with larger instruments is that tissue obtained is sometimes small and friable. With practice, however, cylinders of tissue which provide a good field for mi-

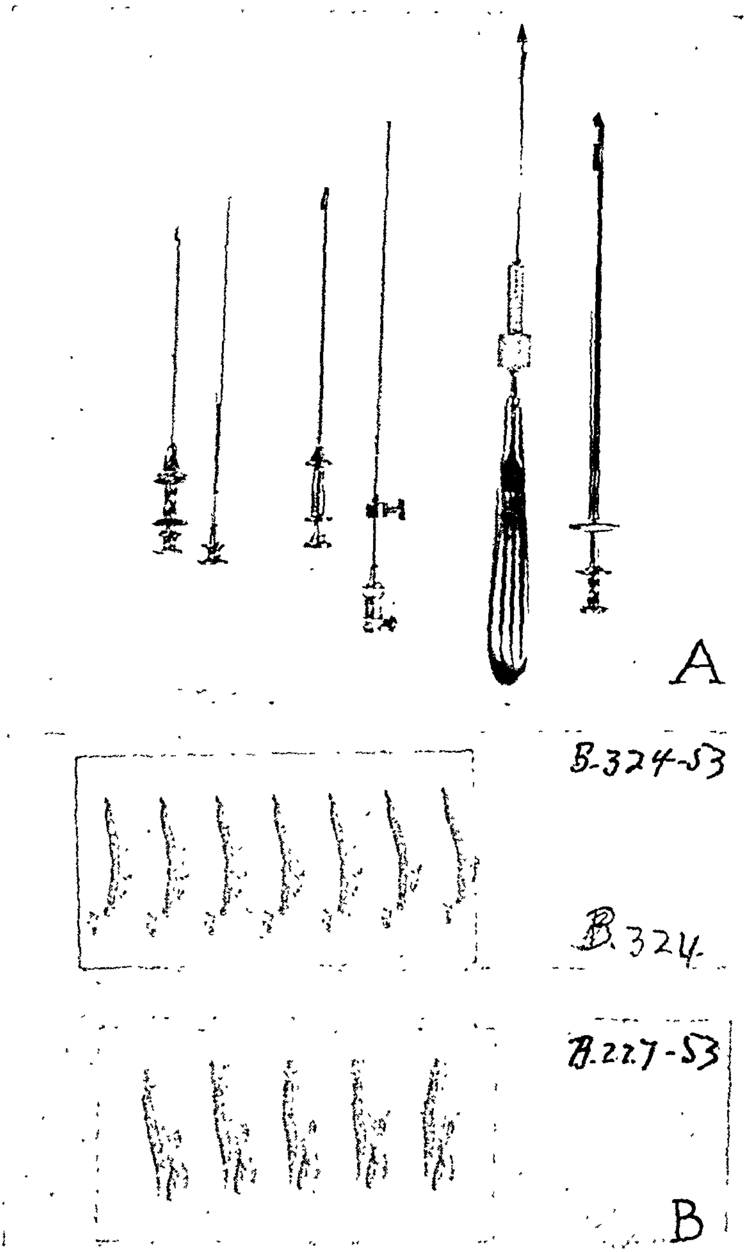

FIG. 3. *A*, prostatic biopsy instruments: Silverman needle, Turkel needle, Veenema punch, and Melick needle. *B*, microscope slides showing multiple sections of Silverman needle biopsies of prostate.

croscopic examination of multiple sections are obtained (figs. 3, *B* and 4). If the biopsy is taken from the critical area, the amount of tissue provided by this relatively small instrument is sufficient to make a diagnosis in most cases.

It was formerly our practice to use the needle with the patient anesthetized and in the exaggerated lithotomy position. A sound was placed in the urethra to depress the prostate. However, in the last 28 cases biopsy was performed under

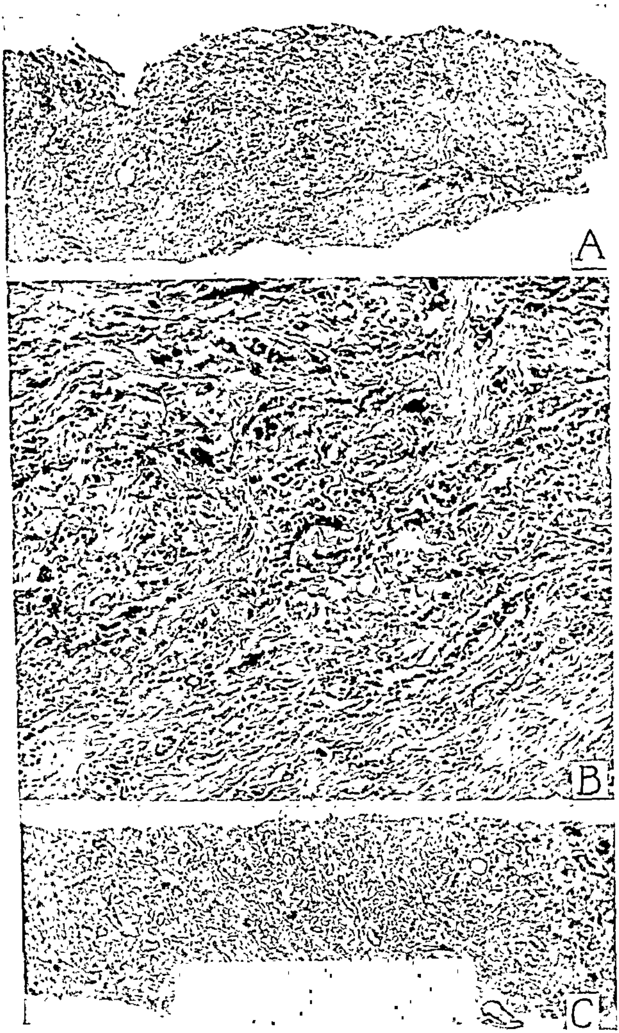

Fig. 4. *A*, low power photomicrograph of Silverman needle biopsy showing carcinoma (×100). *B*, high power photomicrograph of needle biopsy shown in *A* (×400). *C*, needle biopsy showing luxuriant prostatic carcinoma (×100).

local anesthesia with the patient in the ordinary lithotomy position and without a urethral sound. Trilene was used in some cases as a supplementary analgesic In these 28 cases the technique was as follows:

The needle is introduced low in the perineum, near the margin of the anus and a little to the right or left of the midline depending upon the location of the indurated area. The needle penetrates above or through the rectal sphincter and can be felt with the rectal finger for the entire distance as it is being advanced. By keeping the instrument just anterior to the rectum, the exact area of induration can be entered by depressing the outer end of the needle. In the earlier technique normal apical prostate was often penetrated before reaching a nodule at the base. This resulted in uncertainty about the position of the needle tip. An important feature of the method is the advancement of the needle and obturator up to the nodule but not into it. When the inner blades are advanced and extend beyond the end of the outer sheath they penetrate the nodule through its entire diameter and engage tissue from the desired area. The outer needle is then advanced for a distance of 2 to 3 centimeters while the inner blades are held stationary. The outer sheath is then rotated 360° (or the whole instrument is levered up and down) severing the cylinder of tissue at its base (fig. 5, *A*). Figure 5, *B* and *C* are low and high power photomicrographs of a needle biopsy specimen removed from a small nodule of the prostate (group A) by the method described and illustrated. The needle engaged carcinoma tissue proximally and fibromuscular stroma outside of the nodule beyond the carcinoma.

The biopsy can be done without assistance although it is helpful to have an assistant advance the outer sheath while the operator's finger remains within the rectum for additional biopsies.

If the inner blades can be withdrawn with ease, they are removed while the outer sheath is left in place. However, if resistance is encountered, blades and outer sheath are removed simultaneously. Since multiple biopsies are not significantly more traumatic, it is recommended that at least three good cylinders of tissue be removed for study.

4) Open perineal biopsy. This standard method of confirming the diagnosis of clinically suspected carcinoma of the prostate is the only means considered reliable by many urologists and pathologists. Open perineal biopsy was performed in 74 of our 99 cases. The classical Young or Belt's subsphincteric exposure was used. When the surgeon is familiar with the anatomy of the male perineum, the procedure is simple and almost free of complication. It can be done in one half hour or less in most cases. Extensive dissection about the prostate is unnecessary and undesirable. Generous wedge biopsies are taken from the suspected area as well as from other less suspicious areas (fig. 6).*

All of the biopsies in this series were subjected to careful microscopic investigation before the diagnosis of carcinoma was considered definite. Formerly multiple biopsies were submitted for rapid frozen section and radical prostatectomy was decided upon from their evaluation. Frequent difficulties in making a diagnosis from frozen sections have induced us to alter this practice in some cases.

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* Recently we have used the Castroviejo twin-blade knife for this purpose.

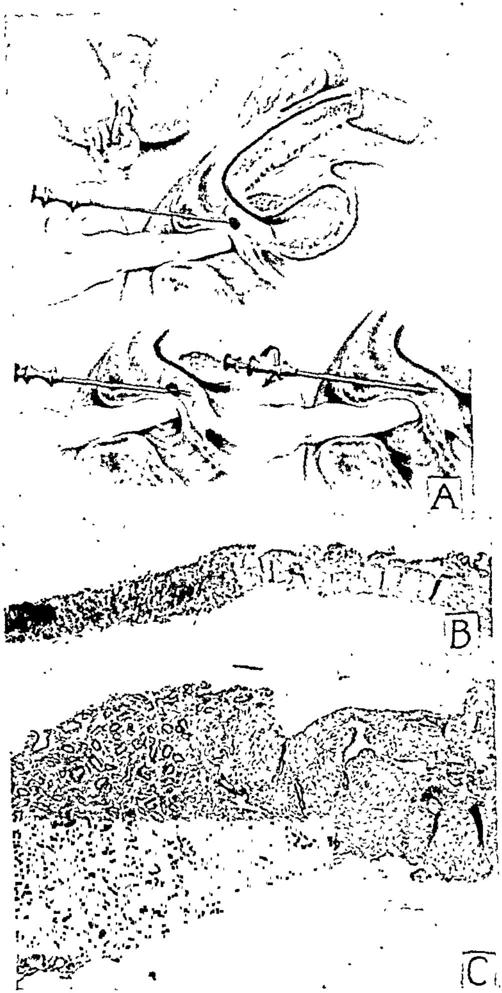

FIG. 5. *A*, artist's drawing of pararectal needle biopsy. Center: needle advanced up to, but not into, nodule. Lower left: obturator removed and biopsy blades advanced into nodule. Lower right: outer sheath advanced and rotated, severing cylinder of tissue at its base. *B*, needle biopsy confirming diagnosis of carcinoma in a small nodule of prostate. Cylinder of tissue contains carcinoma proximally and fibroadenoma distally (×20). *C*, higher power photomicrograph of specimen shown in *B*. Note sharp line of demarcation at border of carcinomatous nodule.

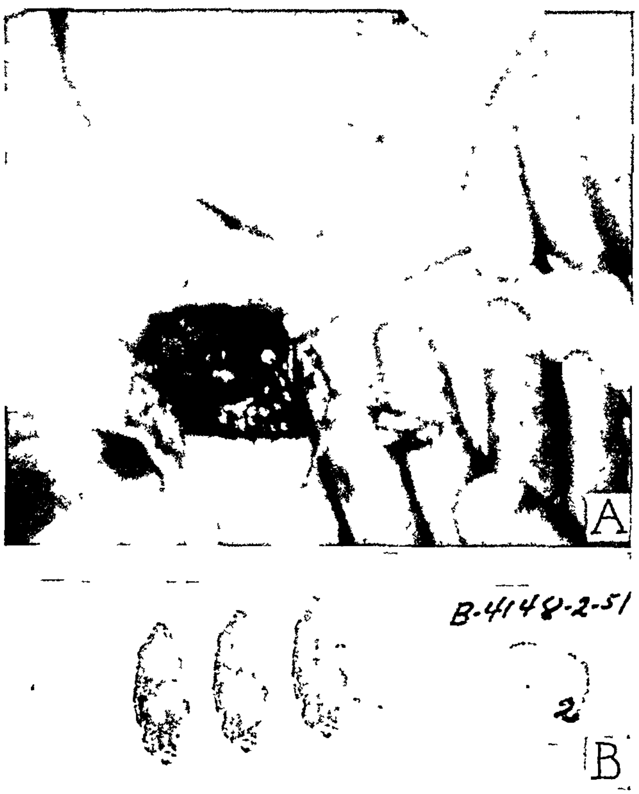

FIG 6. *A*, view of wedge biopsy just taken at open perineal exposure of prostate. *B*, microscopic slide showing size of open prostatic biopsy.

Several biopsies are submitted for multiple paraffin sections and detailed examination. The perineal wound is closed without further delay, and final disposition is made two or three days later when the permanent sections have been reviewed. Young's radical prostatectomy after previous perineal biopsy is as easy or easier than in unoperated cases, provided the operation is done soon after biopsy (2 to 7 days).[21] In the present series this was done on six occasions. It has been illuminating in several instances to find that carcinoma was present in biopsies taken from clinically unsuspected areas while the indurated area felt on digital rectal examination was devoid of tumor.

A distinct advantage of open perineal biopsy is that it affords important information concerning fixation of the prostate, knowledge of which will affect any decision regarding the feasibility of radical prostatectomy.† Five cases which were considered to be in groups A and B on the basis of digital rectal examination were found to have extraprostatic extension on perineal exposure of the gland. These were then treated conservatively.

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† When fixation is present, it is considered in this study to be a definite contraindication to total prostatectomy for purposes of cure In a determined effort to limit Young's radical prostatectomy to truly curable cases in this series, operation was performed in cases of groups A and B only (fig 1).[22]

[21] Goodwin, W. E.· J A.M.A., **148:** 799–803, 1952.

[22] Jewett, H. J.: J. Urol., **61:** 277–280, 1949.

5) *Transurethral resection.* This has been practised only where the clinical findings indicated the need for alleviation of obstruction. The fact that the majority of tumors originate in the posterior portion of the prostate militates against the use of transurethral resection as a biopsy procedure in all but advanced cases. When the method has been used in conjunction with relief of obstructive changes, specimens taken from the posterior portion of the prostate are kept separate for microscopic study. Cuttings from other areas have been isolated for detailed examination when their gross appearance and consistency have suggested carcinoma.[23]

RESULTS

Three groups of comparisons have been made in this study. The standard (100 per cent) has been data obtained from open biopsy or positive transurethral biopsy. The results of clinical impression, prostatic smear and needle biopsy are compared with the results of surgical (open perineal or transurethral) biopsy.

Since the error in palpatory impression was in over-diagnosis of cancer, the percentage of accuracy is expressed in terms of $\frac{\text{Positive Surgical Biopsy}}{\text{Positive Clinical Impression}}$. Positive prostatic smears and needle biopsies can be compared more directly with the results of positive surgical biopsy in the following fashion:

$$\frac{\text{Positive Smear}}{\text{Positive Surgical Biopsy}} \text{ and } \frac{\text{Positive Needle Biopsy}}{\text{Positive Surgical Biopsy}}$$

The results are shown in table 1.

1) *Clinicopathological correlation.* In groups C and D the clinicopathological correlations were 94 and 100 per cent respectively, with an average of 97 per cent. In groups A and B the correlations were 47 and 56 per cent respectively, with an average of 52 per cent.

Only one case of the 99 in this series was considered negative clinically and was proved to have carcinoma on biopsy. This was a case in group B and one in which the needle biopsy was positive.

Sixteen of the 99 cases in this series were considered negative on the basis of *clinical evaluation.* However, there were 35 negative *surgical biopsies* in the series with all of the clinical errors occurring in groups A and B. This indicates that the clinical error was in over-diagnosis of cancer and almost exclusively in the early carcinomas.

There were 11 suspicious smears in this series which were excluded from the positive figures since it was felt that they did not warrant a diagnosis of carcinoma. For a similar reason, four suspicious needle biopsies were excluded. The percentage accuracy figures therefore reflect only those smears and needle biopsies which were considered to show unequivocal carcinoma.

Nine unsatisfactory smears, so considered because of the sparsity of cells, were included in the correlation (and counted as negative values) even when their surgical biopsy counterparts were positive. This reduced the percentage of

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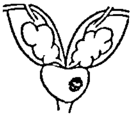
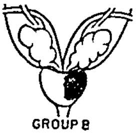
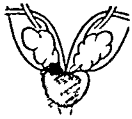
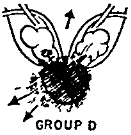
[23] Barnes, R. W., Bergman, R. T. and Farley, S. J. Urol., 57. 755–757, 1947.

TABLE 1

	 GROUP A 27 CASES	 GROUP B 22 CASES	 GROUP C 35 CASES	 GROUP D 15 CASES
Positive open biopsy	7	9	18	6
Positive TUR	0	1	14	9
Total	*7*	*10*	*32*	*15*
Positive clinical impression	15	18	34	15
Accuracy	7/15 = *47%*	10/18 = *56%*	32/34 = *94%*	15/15 = *100%*
Positive prostatic smear	2*	1	8	9
Accuracy	1/6 = *17%*†	1/4 = *25%*‡	8/19 = *42%*§	9/10 = *90%*‖
Positive needle biopsy	5	5	23	13
Accuracy	5/7 = *71%*	5/10 = *50%*	23/32 = *72%*	13/15 = *90%*

* One false positive.
† Smear not done in 1 case proven positive on biopsy.
‡ Smear not done in 5 cases proven positive on biopsy.
§ Smear not done in 13 cases proven positive on biopsy.
‖ Smear not done in 6 cases proven positive on biopsy.

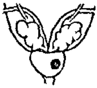
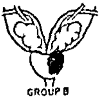
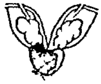
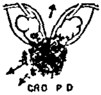
Overall Accuracy		*Accuracy in Groups A and B (Curable)*	
Clinical	74%	Clinical	52%
Smear	45%	Smear	21%
Needle	71%	Needle	61%

accuracy for the smear diagnosis. Similarly, seven needle biopsies containing inadequate prostatic tissue for evaluation, lessened the percentage of accuracy of the needle biopsy. These factors are considered equitable because unsatisfactory smears and needle biopsies are imperfections of the methods.

2) Smear-biopsy correlation. In advanced carcinoma (groups C and D) the correlation was 66 per cent, a figure which is somewhat lower than that achieved by other investigators.[4] In early carcinoma (groups A and B) the correlation was correspondingly lower (21 per cent). It is evident that higher correlations are obtainable in advanced carcinoma which invades the major prostatic ducts or urethra, but that poor comparisons occur when the tumor is small and still confined to the compressed periphery.

3) Needle biopsy-surgical biopsy correlation. The accuracy of needle biopsy was 81 per cent in advanced carcinoma whereas its accuracy was 61 per cent in groups A and B.

TABLE 2

	 GROUP A 7 CASES		 GROUP B 9 CASES		 GROUP C 10 CASES		 GROUP D 2 CASES	
	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg
Surgical biopsy	3	4	3	4	9	1	2	0
Clinical impression	4	3	3*	1†	9	1	2	0
Needle biopsy	3	4	3	4	9	1	2	0

* One case clinically positive was negative on biopsy

† One case clinically negative was positive on biopsy

Clinical accuracy (28 cases)—90 per cent

Needle accuracy (28 cases)—100 per cent

The results of the last 28 needle biopsies are shown in table 2

These highly accurate results of needle biopsy are gratifying and although it is predicted that future biopsies will not continue to show such a precise correlation, we are encouraged by the improvement There are several factors which account for the recently improved results of needle biopsy They are experience, the pararectal approach, and multiple biopsies It is particularly rewarding that the diagnosis was made in six cases of curable carcinoma (groups A and B)

DISCUSSION

The most important factor in the present day diagnosis of carcinoma of the prostate is the palpatory finding of an area of unusual induration We have erred on the side of over suspicion and our mistakes were almost exclusively in groups A and B, properly so, as without suspicion there are no early cases and hence no cures

In this study prostatic smear examination has been less rewarding than needle biopsy in confirming the diagnosis of prostatic cancer Although a fairly high degree of correlation was achieved in the late cases, the results were poor in verifying early carcinoma Our series was too small, however, to warrant an accurate appraisal in this regard It is a method which requires pathologists who are experienced in the special techniques and interpretation and this lessens its popular value Despite the fact that it appears to be "second best" when compared to needle biopsy as a non operative means of confirming the diagnosis of suspected prostatic cancer, the true value of the method may still be in the detection of carcinoma in clinically unsuspected cases [8]*

Needle biopsy has given a high degree of correlation with the results of surgical biopsy in our last 28 cases The accuracy of the needle can be illustrated dramatically by the following case

R A (GH 37547) A 56 year old white man had a painless firm nodule about

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* The relatively poor results obtained from prostatic smear examinations in this study have led us to abandon further use of the Papanicolaou technique for this purpose

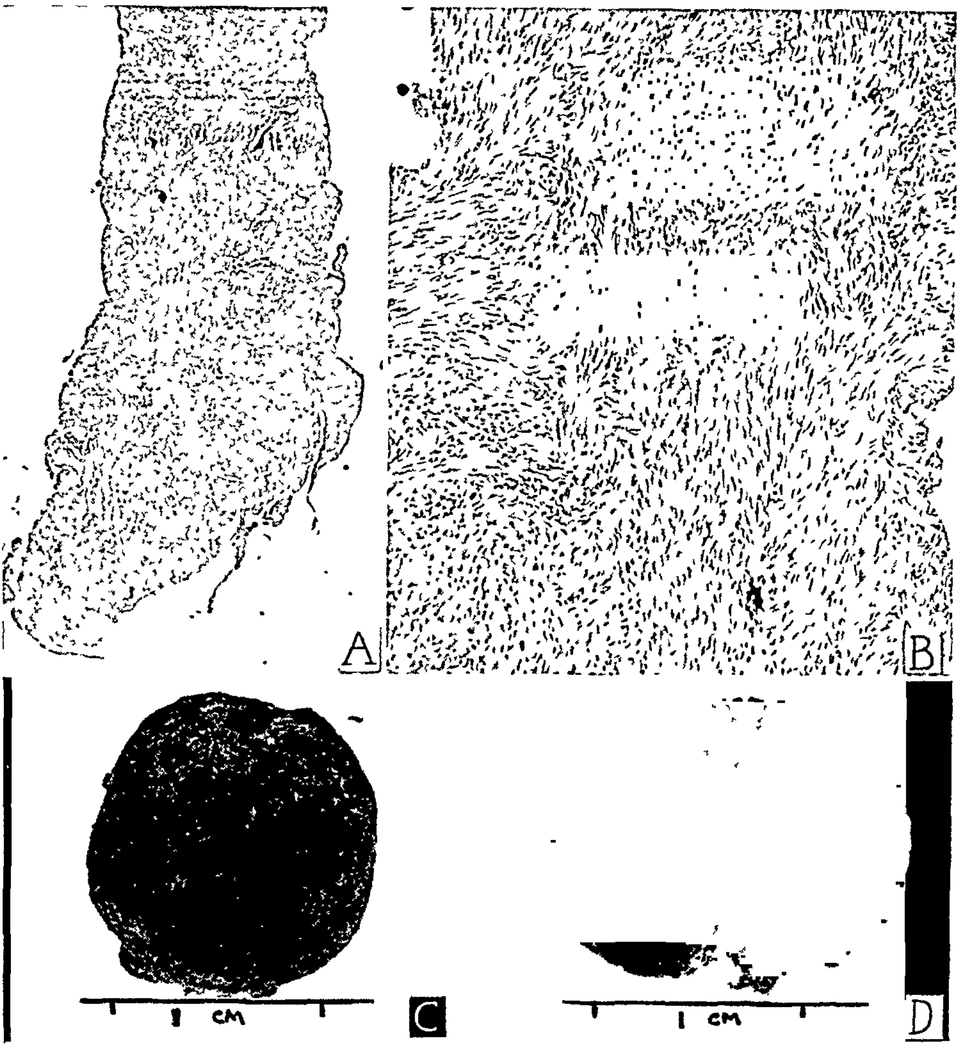

FIG. 7 *A*, needle biopsy taken from a small nodule of prostate. Tissue contains smooth muscle and is devoid of acinar elements (×100). *B*, high power view of biopsy seen in *A*. Note interweaving bundles of smooth muscle fibers and whorl formations. Preoperative diagnosis: leiomyoma of prostate (×400). *C*, leiomyoma shelled out after perineal exposure of prostate *D*, cut surface of leiomyoma showing "watered-silk" lustre.

one centimeter in size on the left lobe of the prostate which was considered to be carcinoma group A. He was otherwise asymptomatic; and bone survey, phosphatase studies, urinalysis, and cystoscopy were negative. Needle biopsy performed under local anesthesia revealed tissue suggestive of leiomyoma, composed of interweaving bundles and whorls of smooth muscle fibers and devoid of acinar elements and collagen (fig. 7, *A* and *B*). With this preoperative diagnosis, perineal exposure of the prostate was done and a leiomyoma measuring 1.3 centimeters in diameter was shelled out (fig. 7, *C* and *D*). This preoperative diagnosis is unique in the collected cases of leiomyoma of the prostate.[24]

[24] Kaufman, J. J. and Berneike, R. R : J. Urol., **65:** 297–310, 1951.

Although there is a high degree of positive correlation between the *clinical impression* and the *surgical biopsy* data, needle biopsy is an important adjunct in the confirmation of the diagnosis of carcinoma of the prostate. It will not compete with open perineal biopsy as a means of ruling out carcinoma, but this does not detract from its other values. It is a procedure which can be done under local anesthesia in the office. It may be particularly helpful, when positive, for the urologist who is unfamiliar with perineal surgery. If a positive result is obtained in cases of groups A and B, one can proceed directly with radical prostatectomy either by perineal or retropubic approach depending upon the choice of the surgeon. If a positive result is obtained in groups C and D, and transurethral resection is not indicated for relief of obstruction, estrogen therapy with or without orchiectomy can be instituted with the assurance of a confirmed tissue diagnosis. It is in the latter groups also that positive diagnosis, achieved without recourse to surgical exposure of the prostate, will be of aid when injection of intraprostatic radioactive colloidal gold or chromic phosphate is considered for palliation. Also, it is a method which can be used when follow-up histologic examinations are desired to evaluate the effects of various palliative treatments in groups C and D (fig. 8, *A*).

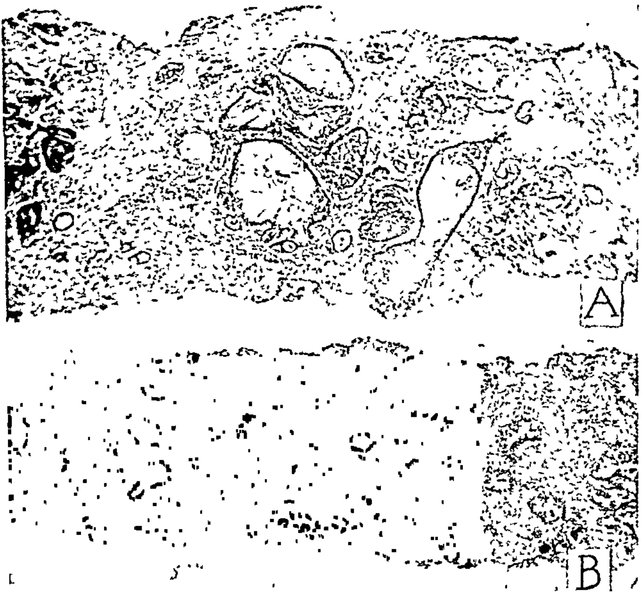

FIG 8 *A*, needle biopsy of prostate in patient previously treated with estrogens. Note squamous metaplasia of prostatic carcinoma. *B*, suspicious needle biopsy. Small compressed hyperchromatic acini are suggestive but not diagnostic of carcinoma (×80).

The greatest usefulness of needle biopsy is to obtain a positive tissue diagnosis in groups C and D. If a negative result is obtained, the urologist should repeat the procedure in two or three weeks. Since the treatment for curable prostatic cancer (Groups A and B) is total excision, open biopsy is still the procedure of choice for definitive diagnosis and treatment in those cases where the clinical diagnosis seems unequivocal. This is vastly preferable to the practise of administering estrogens as a "therapeutic test" and to surmise the presence of carcinoma on the basis of local softening or shrinkage.[15]

Some criticisms have been directed against needle biopsy of the prostate. These deserve mention and clarification. The possibility of implanting carcinoma in the path of the needle seems a remote problem in view of the fact that no such cases have been reported.* Dangers of rectal, bladder, or urethral injury resulting in fistula formation have caused concern to some urologists. In this series the rectum was accidentally entered three times, and the bladder was penetrated on 10 occasions with no untoward sequelae, despite the fact that no special measures were taken following their occurrence. Fort[25] and Grabstald[26] practise transrectal prostatic biopsies, which is further proof that rectal perforation in this procedure is of little consequence. The difficulties in making a positive tissue diagnosis from a needle biopsy specimen have been stressed. However, if several adequate cylinders are taken, sufficient tissue will be available for a pathological interpretation. There are occasional "borderline" cases which will not allow unequivocal diagnosis. However, this is true also of tissue removed by open biopsy and is often inherent in the character of the myriad forms taken by prostatic carcinoma. Specimens containing a few small, compressed atypical acini can only be called suspicious and will require additional needle biopsies, or ultimately open biopsies, for final clarification (fig. 8, *B*). In conclusion, we believe that needle or punch biopsy deserves further study and exploitation as a valuable measure in diagnosing both early and late carcinomas of the prostate.

SUMMARY AND CONCLUSION

Four methods available for the diagnosis of carcinoma of the prostate have been correlated. They are: palpatory findings, prostatic smear, needle biopsy, and open perineal or transurethral biopsy.

Ninety-nine cases of clinically suggestive carcinoma of the prostate were graded according to their degree of suspicion. All of these cases were subjected to needle biopsy and open perineal or transurethral biopsy. Seventy of the same cases had prostatic smear examinations.

Detailed description is given of the para-rectal needle biopsy of the prostate employing the Silverman needle.

A high degree of correlation (74 per cent) was demonstrated between the positive open perineal and transurethral biopsies and the clinical impression in both early and late cases There were many false positives on the basis of clinical impressions in cases suggesting early carcinoma of the prostate

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* A recent article by Clarke, B. G., Leadbetter, W. F. and Campbell, S. J. (J. Urol. 70: 937–939, 1953) reports the first recorded case of implantation of protastic carcinoma in the site of pernieal needle biopsy.

[25] Fort, A.: An. de cir., Rosario, **16:** 213, 1951.

[26] Grabstald, H. and Elliott, J. L.: J.A.M.A., **153:** 563–565, 1953.

The prostatic smear showed an overall positive correlation of 41 with the results of open perineal or transurethral biopsy Greater accuracy was obtained in the late cases An overall accuracy of 71 per cent was shown for needle biopsy when compared with the results of open or transurethral biopsy In the last 28 cases, including six early carcinomas, the needle accuracy was 100 per cent In these 28 cases the accuracy of palpatory impression was 90 per cent

The applicability of the various diagnostic methods in the confirmation of carcinoma of the prostate is discussed

It is concluded that with the rectal finger as a guide in discovering cases of carcinoma of the prostate, and with the biopsy needle as a confirmatory agent, a high degree of accuracy can be achieved in establishing the presence of prostatic cancer Positive diagnosis, thus attained, will often be helpful before instituting palliative treatment in late cases, and may be highly rewarding in disclosing early cases at a time when surgical cure is possible

ADDENDUM

Since this manuscript was submitted several comparable studies have been reported Two of these with results which closely parallel this study are the following Spring, W B and Alden, M W Canad M. A J 70. 179-185, 1954 Colby, F H Urol 69. 797-806, 1953

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TREATMENT OF PROSTATIC CARCINOMA WITH RADIOACTIVE COLLOIDAL CHROMIC PHOSPHATE (P^{32}): A PRELIMINARY REPORT

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It is the purpose of this report to evaluate the therapy and clinical results of the treatment of 28 cases of carcinoma of the prostate treated with colloidal radioactive chromic phosphate during the past year.

Radiation therapy by means of radium and roentgen rays has been used as a form of treatment over a period of many years for certain patients with inoperable prostatic carcinoma. The results reported by Pasteau, Young, Barringer, Deming, Bugbee, Bumpus, and others, included treatment techniques employing deep x-ray therapy externally, as well as the interstitial use of radium and radon alone or combined with external radiation. The prostatic cancer when radiated often showed definite reduction in the tumor mass. Occasionally complete eradication of disease has been reported. More recently when intensive x-ray and radium treatment was employed, most of the treated tumors showed some response. At the same time, with the larger x-ray and radium doses the incidence of complications resulting from the effects of radiation on the surrounding normal tissues increased in number and severity. Bladder irritation and ulceration and damage to the adjacent intestinal loops resulting in radiation colitis, ileitis, and sometimes stricture formation, made the necessary intensive x-ray and radium treatment for this condition impractical.

Flocks, Kerr, Elkins, and Culp (1952) have reported the results of treatment of this disease by the interstitial injection of radioactive gold (Au198). When such in colloidal solution was injected into the site of the prostatic cancer, the authors reported that 90 per cent of the material remained at the site of injection, and that it was apparently nontoxic. Improvements in technique seem to have done away with the moderate rectal irritation which they observed early in their studies. Local spread of the material is induced by the use of hyaluronidase, and the general spread by absorption into the blood is inhibited by epinephrin. One millicurie of radioactive gold per cubic centimeter of tissue represents approximately 65,000 equivalent roentgens of beta dosage together with some six to seven thousand units of gamma roentgens. Since the maximum range of the gold particle is only 3.8 mm. and because about 95 per cent of the effective rays are beta rays, very intensive irradiation of the tumor tissue is possible without danger of damage to the surrounding normal tissues. About one millicurie of colloidal gold-198 is injected into the prostatic area for each gram of estimated weight. This is accomplished by a special lead covered syringe with a rachet device per-

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mitting considerable pressure to be applied and at the same time limits the amount given to a volume as selected by the operator, ranging from 1 to 5 cc.

The first 50 cases treated by these authors and followed from 7 to 17 months had previously been treated by hormones and other procedures without success. The results as reported in the *Journal of Urology* (August, 1952) are as follows:

Average age	69
Previous treatment	29
Complications (all rectal)	15
Alive without clinical disease	27
Alive with clinical disease	8
Dead without clinical disease	7
Dead with clinical disease	8
Biopsies after Au	
Positive—27	
Negative—10	

We were impressed with the results reported by the University of Iowa group, but there were certain features of the gold treatment which we considered unsatisfactory. First, the short half-life of radioactive gold (2.7 days) does not make it practical for shipping from the Atomic Energy Commission plant at Oak Ridge to the West Coast. The second disadvantage of radioactive gold is the presence of gamma rays. These probably do not add sufficient advantage for therapeutic purposes but do definitely present a health hazard to personnel handling the material because of their long range and high degree of penetrability. This necessitates heavy lead shielding (32 lb. lead pot necessary) in shipping, which increases the cost of air freight. The gamma rays in radioactive gold also increase the need for shielding in the operating room while the material is being prepared by the radiologist. It requires a special lead lined syringe for the surgeon in order to protect his hands. To allow for the physical decay during shipping, it is necessary to order a larger quantity of the material. This added quantity requires additional lead-shielding in shipping and further increases the cost of air freight. The possibility of bone marrow depression by the gamma radiation is another disagreeable factor. Recently, four cases have been reported by Botsford, Wheeler, Newton and Jaques (1953), where bone marrow depression occurred from doses of radioactive gold injected intraperitoneally and intrapleurally in ranges over 50 millicuries.

We sought a radioactive substance that could be made in colloidal form with a particle size large enough so that it would not permeate the blood vessels and thus enter the general circulation. We wanted a substance that would have pure beta radiation so that there would be little or no damage to adjacent normal structures and would require a minimal amount of shielding for shipping and safe handling in the operating room. We desired to obtain a substance with a longer half life so that physical decay would not be rapid, and it might be possible to keep the material on hand for use as needed.

Radioactive colloidal chromic phosphate seemed to fulfill all of these requirements. It is made in the laboratory from the soluble form of radiophosphorus (P^{32}). It has a physical decay or half life of 14.3 days. It is a pure beta ray emitter with energy of 0.7 million electron volts. It has a range of 8 mm. of maximum penetration in water or tissue, and it delivers a total dose in roentgen equivalents physical (REP) of 885,000 REP to 1 gm. or cubic centimeter of tissue containing 1 millicurie of the isotope completely disintegrating. The shielding required to protect the surgeon's hands is minimal since beta rays are easily filtered out by plastic, glass and aluminum. The rubber gloves worn by the operator are sufficient to protect the skin of his hands from contact with the beta rays. If there is any contamination of instruments, linen, operating room table or floor, the radioactive material may easily be washed off by means of a detergent soap and water. The handling of the patient postoperatively is safer because there are no long range gamma rays which may cause injury to visitors or to adjacent patients in wards. The effect in the tumor area is that of millions of beta particles of the material each acting as a radiation source which extends its effect over a distance of 8 mm. Theoretically, if one could distribute the material uniformly throughout the cancer area, it would be possible to destroy all of the cancer tissue without injuring the adjacent normal tissues.

Intensive radiation occurs in the immediate area of the injection of the isotope. However, the material may not be taken up by the lymphatics and delivered to the regional lymph nodes, as has been demonstrated with gold. It is questionable whether a lymph gland packed with tumor cells would receive additional radioactive material.

We have seen no deleterious effects from the use of this isotope as far as the general condition of the patient or the bone marrow is concerned. We have monitored the excreted urine and find that 1½ per cent of the injected material is excreted in 24 hours, and only an additional 1 per cent is excreted for the next 6 days. This shows that 97.5 per cent of the material stays at the site of injection. Samples of the patient's blood and bone marrow failed to reveal any radiation activity in these tissues. Very small amount of radiation could be picked up over the spleen, kidneys, and liver. This amount of radiation is not considered large enough to cause any damage to these organs.

When colloidal chromic phosphate was injected into the prostate of dogs, and they were sacrificed between 4 to 5 months, the following changes were noted. The entire prostate was reduced in size, the tissue was firm, avascular, and failed to show any radiation activity. The liver, spleen, kidneys, and lungs showed no deleterious effect or radiation activity. Sagittal sections through the prostate close to the site of the implanted radioactive material revealed scarring and inflammation with areas of necrosis. However, it was remarkable how restricted the effect was in the prostate. The histological examination disclosed a diffuse increase of fibrous connective tissue throughout the organ. The only tubules that showed any effect were in the immediate region of the implanted chemical (figs. 1 and 2, courtesy Dr. Harry Goldblatt). Microscopic sections on liver, kidney, spleen, lungs, and pelvic lymph glands showed no significant changes.

Patients with carcinoma of the prostate may be divided into three states of the disease, dependent upon the clinical findings: 1) when the cancer is limited to the prostate itself; 2) when the tumor extends beyond the prostatic capsule into the periprostatic tissue and regional lymph nodes; 3) when there are distant metastases. Unfortunately, the number of cases of carcinoma of the prostate in

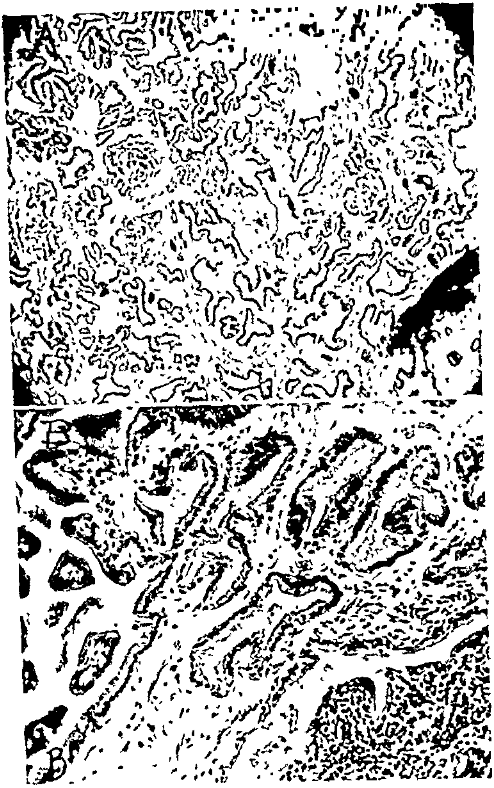

FIG. 1. *A*, low power photomicrograph of section of prostate of dog 1 cm. from site of injection. *B*, high power, same section.

stage one is small, approximately 5 per cent. In these patients the disease is discovered either by a routine rectal examination or at the time of transurethral resection. The treatment of choice in this stage is total prostatectomy.

A much larger number of patients present themselves in the second stage of the disease. Symptoms of bladder neck obstruction are usually present, and the examination reveals a fixation of the gland with extension of the lesion along the seminal vesicles. Occasionally regional lymph nodes are involved. However, no evidence of distant metastases are demonstrated. The treatment suggested in these cases has been transurethral prostatic-resection and hormonal therapy. Approximately 50 to 60 per cent of the patients with prostatic cancer present themselves in the second stage of the disease.

The patients seen in the third stage of the disease have all the findings of those

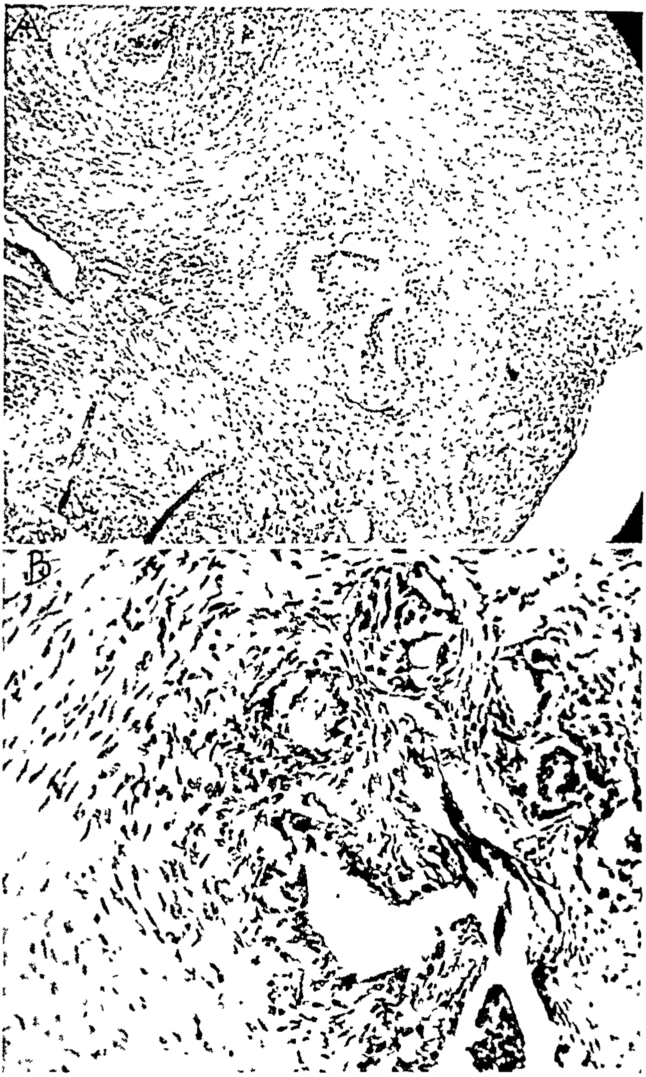

FIG. 2. *A*, low power photomicrograph of section of prostate of dog at site of injection. *B*, high power, same section.

in the second but in addition have distant metastases (osseous and lungs). The treatment in these patients has been transurethral resection of the bladder neck, estrogens, orchiectomy, and high voltage irradiation for relief of pain.

TECHNIQUE OF INJECTION

The perineal approach to the prostate for carrying out interstitial irradiation of the gland was found unsatisfactory because it does not permit adequate exposure of the prostate and the regional lymph nodes. However, it has been suggested that the prostate be injected from both approaches in order to obtain a more thorough distribution of the isotope. In three of the patients, metastatic masses 2 and 3 cm. in diameter were encountered. In only one was the mass removed. A biopsy was always taken of the involved nodes, and an attempt was made to thoroughly infiltrate all palpable nodes with the radioactive material.

It has been observed that in the smaller prostates the response has been better. Therefore, an increasingly larger amount of prostatic tissue has been removed transvesically before carrying out the injection, and the number of points of injection have also been increased.

After the bladder is opened a finger is placed in the rectum, making palpation of the prostate gland possible, to determine the local extension of the disease, the consistency and size of the prostate (weight in grams).

It is on this basis that the amount of radioactive material to be injected is calculated. A second biopsy of the prostate is always obtained at this time, and a revision of the bladder neck is carried out when obstruction is present. Multiple 21 caliber spinal puncture needles are inserted transvesically into the substance of the prostate, seminal vesicles, periprostatic tissues, and involved regional lymph nodes. The use of multiple needles has the advantage of obtaining more even distribution of the material, and in addition the immediate knowledge of direct entrance into a blood vessel, thus avoiding introducing of the material into the blood stream. Following the placing of the needles, the finger is removed from the rectum, making two hands available for manipulating the syringe, a distinct and welcome advantage. The radiologist is always in attendance to calculate and to prepare the material to be injected in each case. The solutions contain from 1 to 3 millicuries of chromic phosphate per cubic centimeter. To the isotope there is added 100 TU of hyaluronidase in 1 cc of 1:1000 epinephrine. Approximately 0.3 to 0.5 millicuries are injected for each gram of tissue; the largest amount injected in any single case was 40 millicuries.

A special syringe has been designed which permits the use of disposable glass

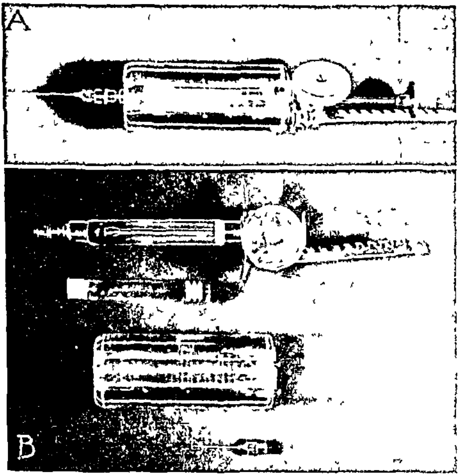

FIG. 3 Special syringe for injecting radioactive chromic phosphate into prostate. It is designed for use of disposable glass cartridges

cartridges. The material is packaged in these cartridges and therefore the loading of each syringe at the operating table is unnecessary. This minimizes the danger of contamination of the operator and operating room equipment. The syringe is shielded by a plastic cover which is adequate to filter out the beta rays (fig. 3).

The bladder is closed and drainage is maintained by an indwelling urethral catheter for 5 days.

The first 28 patients with cancer of the prostate who have been treated with chromic phosphate (P^{32}) are presented. The patients chosen for treatment were considered in stage two of the disease. With two exceptions they had all received estrogens from six months to two years. Eight cases had bilateral orchiectomies prior to treatment.

RESULTS

Ages of patients, from 54 to 81.

Symptoms: Bladder neck obstruction, 8; acute retention, 13.

Previous surgery: Transurethral prostatic resection, 13; bilateral orchiectomy, 8; permanent suprapubic cystostomy, 2.

Unilateral or bilateral extension to the seminal vesicles: 28.

Acid phosphotase: Elevated in 6.

Amount of radioactive material introduced: 6 to 40 mc. chromic phosphate (P^{32}).

Number of deaths: 4. Cardiac arrest, 1; pulmonary embolus, 1; coronary, 2.

CLINICAL COURSE

Change in size of prostate: None in 10; decrease in 18. Change in consistency of prostate: Softening, 4; firmer, 14. Postoperative biopsies: 3 months, 10; 12 months, 1.

Although sufficient time for detailed evaluation has not elapsed, the clinical results of treatment in this small group of cases have been interesting and encouraging. In 14 cases there was a remarkable decrease in the size of the gland and a definite change in consistency of the prostate within 30 to 60 days following treatment. Fifteen patients experienced a gain in weight and a general feeling of well-being. In 2 patients osseous metastases developed following treatment, one at six months, and the other at 4 months, respectively.

The microscopic findings are neither as striking nor as encouraging as the rectal and clinical findings. A biopsy with the perineal needle or transurethrally was obtained in all cases before treatment. A second was obtained transvesically at the time of injection of the isotope, and a third three to four months postoperatively. Tissue removed at 3 months was radioactive. Only ten of our patients have been treated more than six months, therefore postoperative biopsies have not been obtained in the other eighteen. In only one other case was a biopsy taken at 6 months. There was evidence of tumor in all biopsies. After a study of many sections in each patient, it was evident that there are histological changes in the radiated tissue when compared to the specimen of tumor obtained before treatment. Some sections revealed the presence of diffuse fibrosis and areas of necrosis. The nuclei of the malignant cells appear hypochromatic, irregular and shrunken, consistent with dying cells. However, in other areas in the same sections the tumor cells appear healthy and apparently are growing actively. The patient who has survived more than 12 months, is in excellent general health, without evidence of metastases. The prostate is small, firm, and fixed. The sections of tissue removed prior to treatment show epithelial cells arranged in strands, *columns with small acini. Diagnosis, adenocarcinoma (fig. 4). Sections of tissue* obtained at 3 and 6 months after interstitial radiation with chromic phosphate showed many areas of increased fibrosis, with areas of necrosis and inflammation. At 12 months there was extensive fibrosis throughout areas of the sections, and large masses of tumor cells revealed radiation changes. However, it is not possible to say from the histology that the tumor was destroyed in a single case (fig. 5).

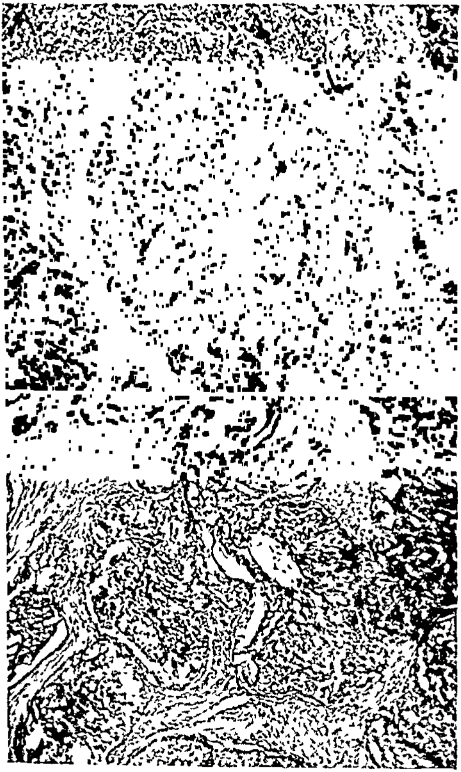

FIG. 4. *A*, low power photomicrograph of section of prostate, of patient alive over 12 months, prior to treatment. *B*, photomicrograph of a section of prostate, same patient, 3 months following treatment.

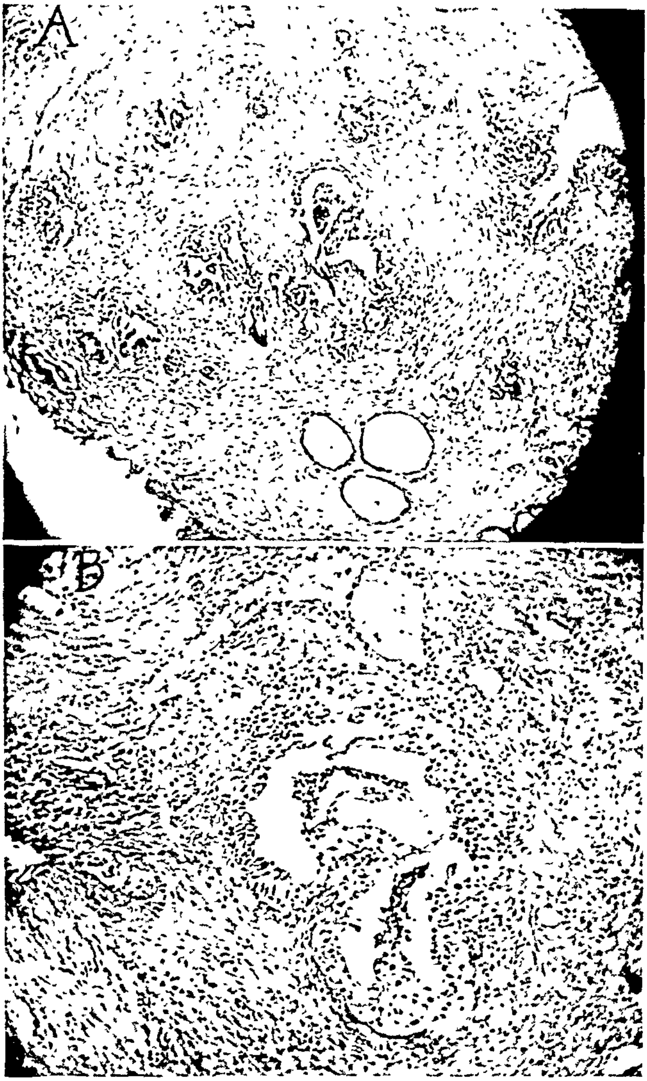

FIG. 5. *A*, low power photomicrograph of section of prostate, 12 months following treatment, showing marked fibrosis and atypical glandular formation. *B*, high power section reveals same advance radiation changes, but cells are present which can not be distinguished morphologically from tumor cells.

The marked scarring, necrosis, and diffuse fibrosis with the cellular changes which have been observed close to the site of the implanted radioactive material both in man and animal suggest that with thorough dispersion of radioactive chromic phosphate (P^{32}) throughout the organ, destruction of prostatic cancer should be obtained.

COMPLICATIONS

No serious complications have developed thus far. Some of the patients with edema of the rectal wall have complained of bowel irritation. Mild bladder symptoms have occurred in nearly all patients. These discomforts have subsided within 30 to 40 days. Immediate blood studies revealed a very small amount of material present, but there have been no late changes demonstrated in either blood or bone marrow. One patient, who died of pulmonary embolus after 5 days, showed radioactivity in the prostate and the associated pelvic tissues. The liver was radioactive. No evidence of radioactivity was noted in the spleen, kidneys, or lungs. An assay of the liver for the radioactivity content is being undertaken to determine the amount of material contained in this organ.

The authors wish to extend their gratitude to Mortimer E. Morton, Chief of Radioisotope Unit, Veterans Hospital, Long Beach, for his valued assistance and sedulous effort.

SUMMARY

Preliminary experience with the treatment of 28 cases of carcinoma of the prostate using colloidal radioactive chromic phosphate has been reported. Interstitial radiation of cancer of the prostate in stage two of the disease using radioactive isotopes emiting beta radiation, seems encouraging.

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INTRAPROSTATIC INJECTIONS OF RADIOACTIVE COLLOIDS: II. DISTRIBUTION WITHIN THE PROSTATE AND TISSUE CHANGES FOLLOWING INJECTION IN THE DOG

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The recent availability of radioactive materials has led the urologist to search for substances which would be effective in destroying or controlling neoplasms of the prostate gland and bladder.

Radioactive colloidal gold injections, as a therapeutic measure have been advocated by Flocks and Kerr.[1] Their preliminary reports offer sufficient encouragement to prompt further and more extensive investigation.

After inspecting some of the clinical work of Dr. Flocks at Iowa City, we felt that additional experimental work, using dogs, might be helpful in clarifying some of the unanswered aspects of this problem. Two phases of the problem seemed important. Since we were unable to find any published reports detailing the distribution and excretion of the radiocolloids following injection into the prostate gland, we felt it would be worth while to undertake such studies in dogs. The detailed findings of this study have been made the subject of another preliminary report.[2]

The present report is an attempt to record exactly what occurs locally in the prostatic tissue as well as in distant organs of the dog after injections of radiocolloids. Early and late tissue changes as well as distribution of the material within the prostatic capsule have been studied. Additional observations will be reported after a still longer period has elapsed.

Radioactive colloidal chromic phosphate (P^{32}) was used in these studies as well as radioactive colloidal gold (Au 198), since we felt that radioactive phosphorus offered several theoretical advantages.

Radiophosphorus, which has a half-life of 14.3 days and emits only beta particles with maximum energy of 1.7 m.e.v., has many advantages over radiogold which has a half-life of 2.7 days and emits 0.95 m.e.v. beta rays and 0.74 m.e.v. gamma rays. The absence of gamma rays makes the handling of radiophosphorus simpler and the radiological hazard to the personnel less. The longer half-life and higher energy of the beta rays of radioactive phosphorus result in a more prolonged and greater radiation than can be achieved with radiogold, using an equal concentration per gram of tissue. Complete disintegration of one

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TABLE 1 *Comparison of radiation delivered by radioactive phosphorus and radioactive gold*

	FRACTION OF DECAY IN FIRST 24 HOURS	EQUIV ROENTGENS DELIVERED IN FIRST 24 HOURS*	TOTAL EQUIV ROENTGENS DELIVERED*
Au 198	0 23	19 3	84
P 32	0 017	11 6	885

* These figures are calculated for a dose of 1 microcurie per gram of tissue to complete disintegration

microcurie of P^{32} per gram of tissue will deliver a radiation dose of 885 equivalent roentgens (e r), while the same amount of Au 198 will deliver only 76 e r of beta radiation The gamma ray contribution from gold is difficult to assess with certainty, but is of the order of 8 r per microcurie disintegrating[3] per gram of tissue Thus, it is possible to deliver approximately ten times the radiation dosage with radioactive phosphorus as compared with radioactive gold The range of the beta particles from radiophosphorus is about double that of radiogold The longer half-life of P^{32} permits a longer period of storage before use

The advantages of gold lie in whatever contribution the gamma radiation has to wider radiation of tissue For large doses of radiogold, the roentgens delivered to the gland by gamma rays alone may be in the cancericidal range This is important, if homogenous distribution in the gland cannot be achieved, since the effect of beta radiation is limited to a small volume surrounding the colloid The apparent greater uniformity and stability of the gold colloid and the lesser tendency to form larger aggregates may also be advantageous See table 1

METHODS

Ten dogs were injected with colloidal chromic phosphate and nine with colloidal gold The methods of injection and preparation of material are described in detail elsewhere[2] Animals were sacrificed at intervals of two weeks to three months in the case of phosphorus, and intervals of one week to seven weeks in the case of gold All organs were examined carefully both grossly and microscopically Tissues were prepared in the usual way, using paraffin embedding for sectioning and were stained with hematoxylin and eosin Fat stains were also done on the livers to detect possible liver damage The prostates injected with gold were also stained by the method of Elftman and Elftman[4] to better visualize the colloidal particles of this material Serial sections of the prostates were made in order to determine the distribution of colloid in all areas of the gland See figure 1

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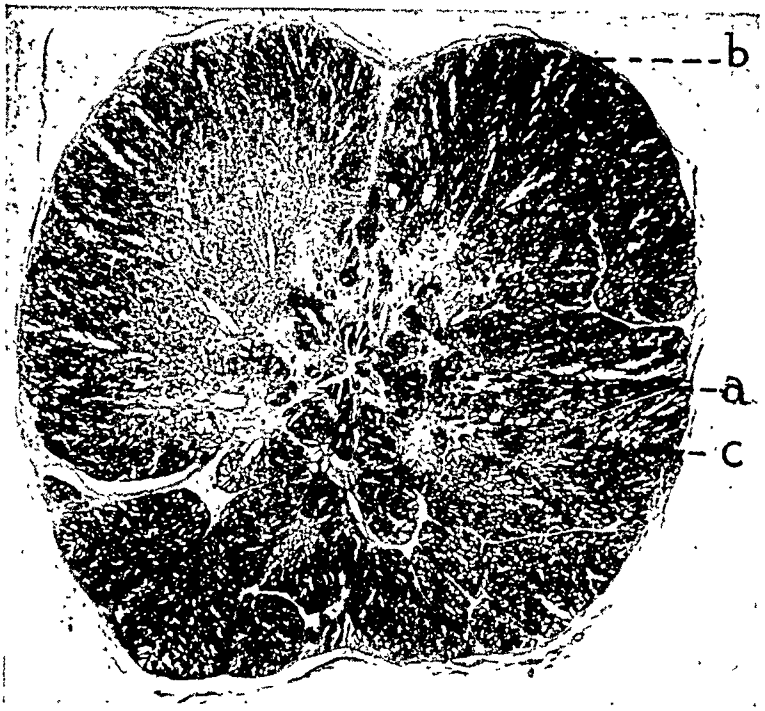

FIG. 1. Normal dog prostate

RESULTS

A. Radioactive colloidal chromic phosphate (P^{32}). The animals in this group showed no abnormal gross or microscopic findings except those to be described in the prostate gland and its investing layers. The regional lymph nodes were grossly unchanged and showed little, if any, radiation reaction.

There were a moderate number of periprostatic adhesions, more marked in the animals that had had extravasation of the radiogold at the time of injection. All of these adhesions were filmy and easily broken up by the finger. The prostate, itself, showed areas of subcapsular hemorrhagic reaction at two to five weeks. Serial sections of the gland revealed that the material had not been distributed uniformly throughout the tissue as we had hoped it might be, but that large areas of the gland were completely free of change. This was true in all of the prostates examined in spite of efforts to reach every part of the gland by the injecting needle.

Microscopically (figs. 2, 3 and 4), the reaction to radiophosphorus was marked first by acute necrosis, moderate hemorrhage and slight exudative reaction. The necrosis involved both fibrous and connective tissue as well as epithelial elements. The vessels showed a proliferative intimal arteritis with necrosis of the wall. This acute radiation reaction was very effective in destroying tissue, but it was even more apparent microscopically that much of the normal prostatic tissue remained unchanged. The acute reaction subsided after five to six weeks and healing became apparent at this time, and was fairly complete at the end

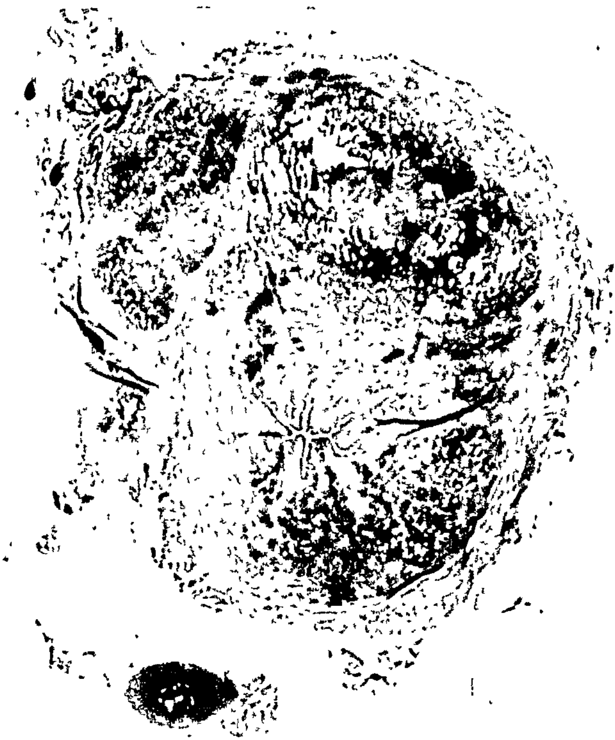

FIG. 2 Dog No 1, five weeks after injection Acute necrosis and hemorrhage following injection of radioactive phosphorus Note incomplete distribution

of three months. Healing by scar formation gave the picture of increased connective tissue, decreased or absent glands, pigmentation, cystic dilatation of nearby glands, and, in some areas, hyalinization. We were able to find normal glands in the center of an area of hyalinization in several cases, indicating that destruction had not been complete even in the center of the most marked radiation reaction.

B. Radioactive colloidal gold (Au 198). The animals in this group showed a much more marked periprostatic reaction as well as evidence of radiation effect in the regional lymph nodes. The dogs sacrificed at one and two weeks showed considerable edema of the periprostatic fat and enlarged hemorrhagic iliac lymph nodes. Those sacrificed at four and seven weeks had firm fibrous adhesions to the prostate and the gland was removed with difficulty for this reason. The lymph node change was quite prominent in this group. In the dogs injected with radiophosphorus, we had difficulty at autopsy in finding suitable regional nodes

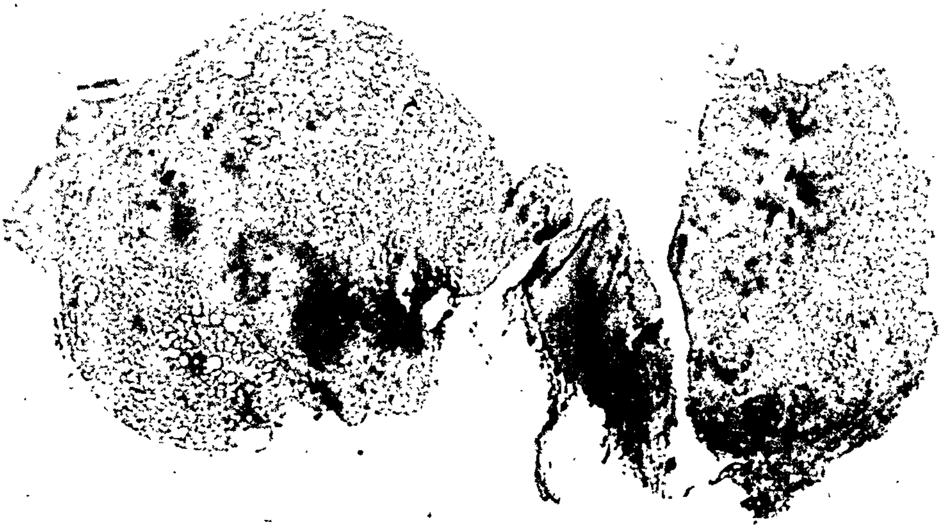

FIG. 3. Dog No. 6, two weeks after injection. Section showing acute radiation reaction to P 32 in a definite path through center of gland.

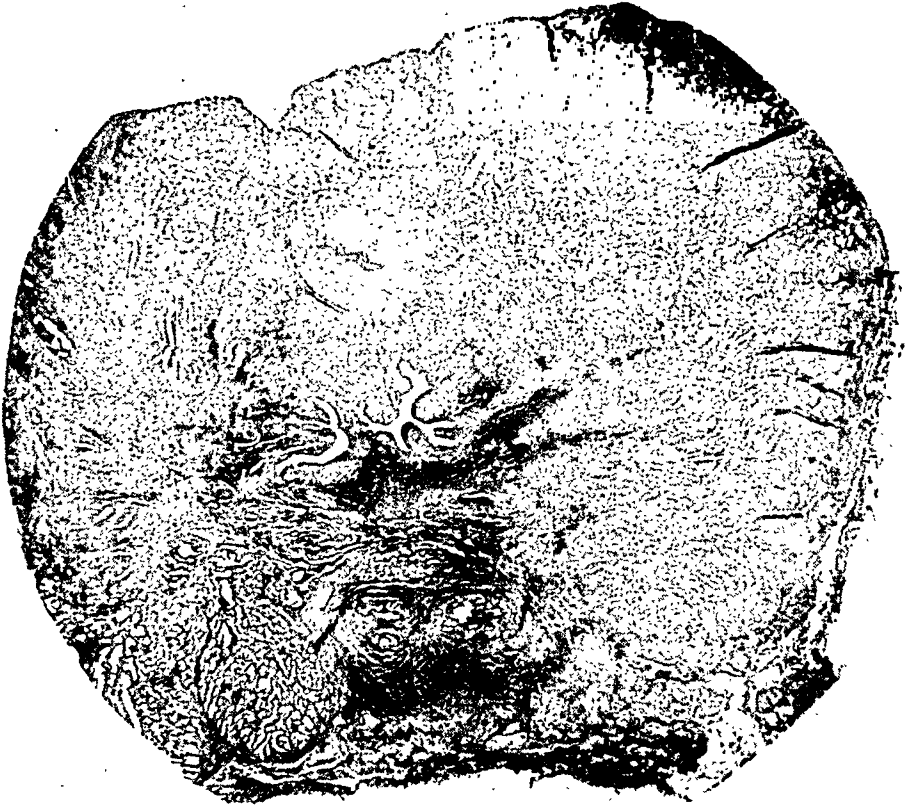

FIG. 4. Dog. No. 3, three months after injection of P 32. Section to show healed lesion with hyalinization and fibrosis. Note normal prostatic glands still present.

of any size for section, but, in the dogs injected with radiogold, these lymph nodes were enlarged two to three times, and, in most cases, hemorrhagic. Serial sections of the prostate, itself, showed a more marked capsular reaction, but about the same patchy pattern of distribution as we had observed in the case of radioactive phosphorus.

Microscopically (figs. 5 and 6), the acute reaction to radioactive gold was quite different from that observed in the previous group. Sections of prostates removed at one and two weeks showed an acute suppurative reaction with exudate in the glands and connective tissue. There were only small areas of hemorrhage and

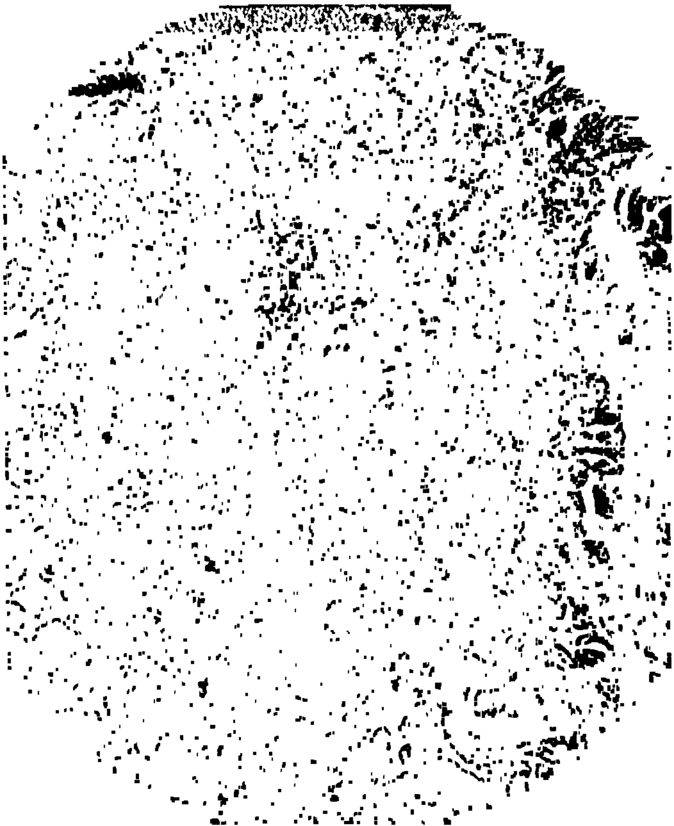

FIG. 5. Dog. No. 14, one month following injection of Au 198. Section to show acute radiation reaction resulting from injection of radioactive gold. Note exudative type reaction as contrasted with figure 2.

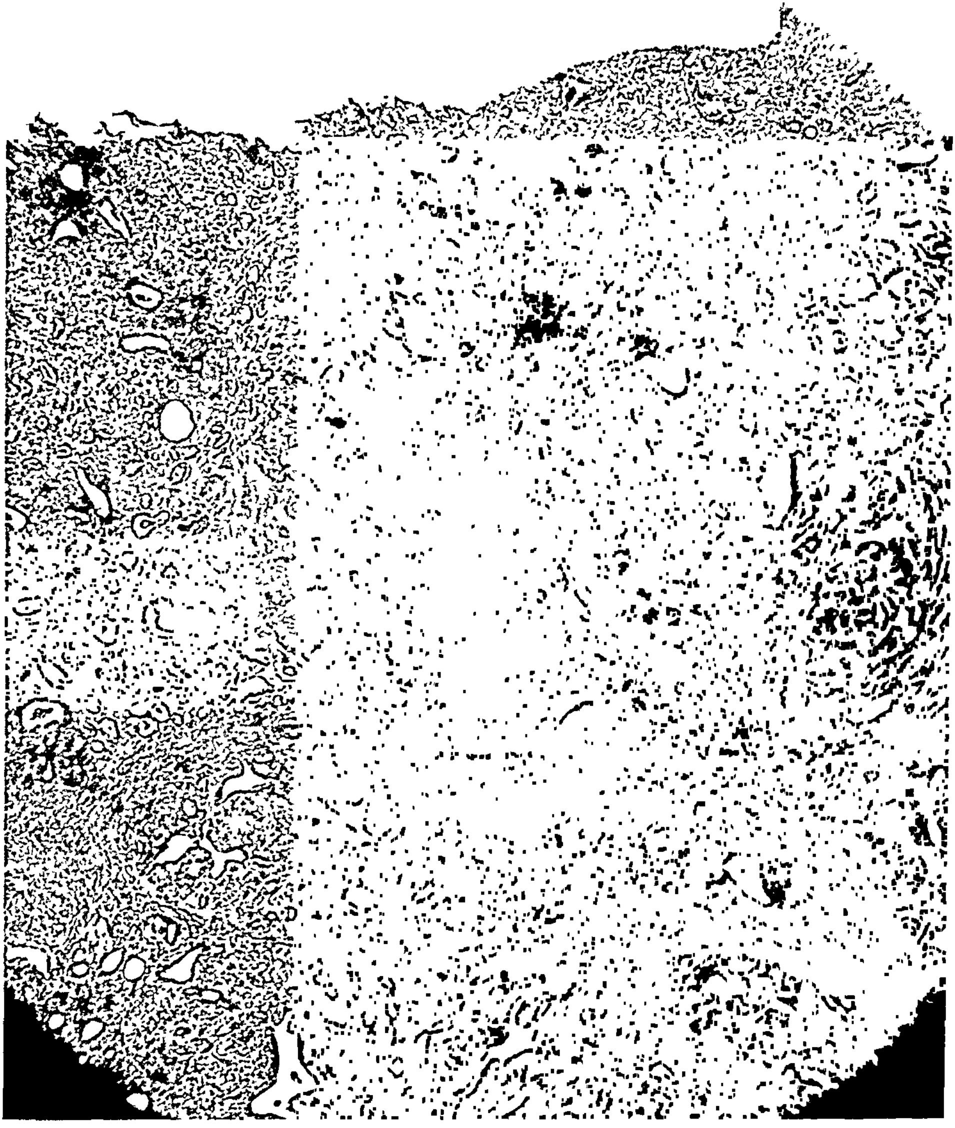

FIG. 6. Dog No. 13, seven weeks following injection of radioactive gold. Section to show late result following injection of radioactive gold. Area of scar surrounded by normal prostatic gland.

necrosis. The peritoneal reaction was more marked. The entire picture was that of an acute exudative reaction, and, at first, we thought we were dealing with a bacterial prostatitis. However, this suppurative type of reaction was a constant finding in all the five animals sacrificed at one and two weeks, and we feel that it represents the radiation reaction to the radioactive colloidal gold Later results, microscopically, were very similar to those observed with phosphorus. Healing took place by scar formation with an increase in connective tissue which replaced the glands destroyed. Again we were able to find normal glands in the midst of this scar tissue, indicating that the radiation effect had not been sufficient to destroy all of the prostatic glands, even where one would expect a maximum effect

The liver and spleen showed no microscopic change in spite of the pickup of considerable radioactive material[2] Other tissues were also unchanged grossly and microscopically

DISCUSSION

It became apparent early in this study that our main problem was to achieve equal and uniform distribution of the colloidal material throughout the prostate gland In the case of both radioactive gold and phosphorus, there was found to be little diffusion away from the path of the needle in spite of the addition of relatively large amounts of hyaluronidase and attempts to improve the technique by moving the needle to all sections of the gland The material in many cases had apparently diffused out into the subcapsular space so that we found a marked capsular radiation reaction and periprostatitis, but many areas of prostate entirely free of change Since many of the prostates weighed only five to ten grams, and were easily accessible at the time of injection, we had expected to achieve a fairly complete destruction of the entire prostate We estimated roughly that we had destroyed as little as 15 per cent of the total prostate gland in some animals and as much as 75 per cent in others, but in none of these animals had we achieved complete destruction of tissue within the prostatic capsule Flocks,[1] in his report on radioactive gold injected into human prostatic carcinoma, apparently experienced similar difficulties in distribution which he mentions in this report This lack of distribution in the human is also borne out by the fact that he has been able to show radiation effects in only about half of the biopsies made after injection of radiogold into prostatic carcinoma [5] It would seem from our studies on the dog that further efforts should be made to improve the technique of injection or the composition of the material, in order to insure a more complete distribution of the colloidal particles throughout the gland

The lack of demonstrable damage to liver, spleen or other organs, in spite of relatively large pickup of radioactive material,[2] would seem to indicate that the materials are safe to use locally without fear of serious side effects If a method can be devised to keep more of the radioactive material within the prostatic capsule, the possibility of damage to distant organs will be even less

The lymph node changes, both grossly and microscopically, were quite prominent with radioactive gold, and this may be a definite advantage to the use of gold in cases of carcinoma of the human prostate with lymphatic spread Little radiation change in the regional lymphatics was observed in the case of animals injected with radioactive phosphorus These observations were borne out by the findings of much greater radioactivity in regional lymph nodes of animals injected with radiogold [2]

The difference between the acute radiation effects of the two materials was quite striking Radioactive chromic phosphate caused an acute necrosis and

[5] Flocks, R H Personal communication

hemorrhagic reaction with little exudative reaction. Radioactive gold, on the other hand, caused an acute exudative reaction with little necrosis or hemorrhage. This difference is difficult to explain. The late reaction of tissue to the two materials was quite similar.

CONCLUSIONS

The injection of radioactive colloidal chromic phosphate (P^{32}) and radioactive colloidal gold (Au 198) into the prostate of the dog causes no appreciable radiation effect in organs distant from the prostate. The only exception to this statement occurred in the case of the regional lymphatics following the injection of radiogold.

Distribution of the colloidal material throughout the prostate was not uniform in any instance, and in none of these animals was destruction of the normal prostate complete. Periprostatic reaction was marked in the case of both materials, but more prominent following the injection of radioactive gold. When healing had occurred, large numbers of normal prostatic glands remained, and, in some cases, normal glands persisted within the center of the healed radiation scar. This was true following injection of both radioactive gold and radioactive chromic phosphate.

The acute radiation reaction occurring in the dog's prostate to radioactive phosphorus differs from that seen due to radioactive gold, but the long term result is about the same following injection of either material.

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CORTISONE TREATMENT IN ADVANCED CARCINOMA OF THE PROSTATE

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Intense interest has arisen in the role of the adrenal glands in carcinoma of the prostate, stimulated by Huggins' work with bilateral adrenalectomy [1 2 3]

In 1950, Sprague[4] in reviewing and discussing the physiologic effects of cortisone brought out, first, that cortisone causes a depression of the endogenous production of adrenal cortical hormone, second, that experimentally, cortisone causes atrophy of the adrenal cortices in rats and, third, that a depression of urinary 17-ketosteroids occurs with the administration of cortisone Wilkins et al [5 6] demonstrated this clinically by showing excellent results with cortisone in children masculinized by congenital adrenal hyperplasia

It therefore seemed reasonable to us that the use of relatively large doses of cortisone in patients with advanced prostatic carcinoma might produce a "medical adrenalectomy" that could be as effective as actual surgical bilateral adrenalectomy We also believed that this would give us an opportunity to study some of the still unknown factors existing in the hormonal interrelationship present in prostatic cancer Taylor et al [7 8 9] in 1950 had reported on the use of ACTH and cortisone in a wide variety of malignancies including a few cases of prostatic cancer but no detailed and extensive studies of carcinoma of the prostate had been reported at the time we undertook this study Since then, there has been a case report in the literature[10] and more recently Harrison, Thorn,

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Supported by Institutional Grant, American Cancer Society Cortisone acetate (Cortone) was generously supplied by Merck & Co Inc

[1] Huggins, C and Scott, W W Bilateral adrenalectomy in prostatic cancer, clinical features and urinary excretion of 17 ketosteroids and estrogens Ann Surg , 122: 1031–1041, 1945

[2] Huggins, C and Bergenstal, D M Surgery of the adrenals J A M A , 147: 101–106, 1951

[3] Huggins, C and Bergenstal, D M Inhibition of human mammary and prostatic cancers by adrenalectomy Cancer Research, 12 134–141, 1952

[4] Sprague, R G and others Observations on the physiologic effects of cortisone and ACTH in man Arch Int Med 85 199–258, Feb 1950

[5] Wilkins, L , Lewis, R A , Klc
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[7] Iorris, R S , Jr Cortical steroids in treatment of cancer, observations on effects of pituitary adrenocorticotropic hormone (ACTH) and cortisone in far advanced cases J A M A 144 1058–1064, 1950

[8] Taylor, S G III and others Effect of ACTH and cortisone on advanced malignant disease Al
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[9] Taylor
ACTH in certain types of malignancy
Proc 1st C
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[10] Havw [illegible] The treatment of late relapse in prostatic carcinoma by cortisone J Urol 69 152 156, 1953

[11] Harrison J H , Thorn G W and Jenkins, D Total adrenalectomy for reactivated carcinoma of the prostate N Eng J Med , 248 86–92, 1953

hemorrhagic reaction with little exudative reaction. Radioactive gold, on the other hand, caused an acute exudative reaction with little necrosis or hemorrhage. This difference is difficult to explain. The late reaction of tissue to the two materials was quite similar.

CONCLUSIONS

The injection of radioactive colloidal chromic phosphate (P^{32}) and radioactive colloidal gold (Au 198) into the prostate of the dog causes no appreciable radiation effect in organs distant from the prostate. The only exception to this statement occurred in the case of the regional lymphatics following the injection of radiogold.

Distribution of the colloidal material throughout the prostate was not uniform in any instance, and in none of these animals was destruction of the normal prostate complete. Periprostatic reaction was marked in the case of both materials, but more prominent following the injection of radioactive gold. When healing had occurred, large numbers of normal prostatic glands remained, and, in some cases, normal glands persisted within the center of the healed radiation scar. This was true following injection of both radioactive gold and radioactive chromic phosphate.

The acute radiation reaction occurring in the dog's prostate to radioactive phosphorus differs from that seen due to radioactive gold, but the long term result is about the same following injection of either material.

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3 *Acid and alkaline phosphatase findings* Four of the 10 patients initially had elevated serum acid phosphatase and 3 of these showed definite and consistent decrease, in one to normal levels Two of these patients had improvement in their local lesion but one of the two had no symptomatic improvement Two of the 10 had a marked progressive increase in acid phosphatase and yet both had wonderful symptomatic relief and improvement in their local lesion The remainder had no essential change in acid phosphatase Thus there seems to be no particular relationship between changes in the acid phosphatase and symptomatic improvement or change in the local lesion

Two of the patients with initially elevated levels of serum alkaline phosphatase had a definite and progressive increase, while the remainder had no essential change

4 *Improvement in bony metastases by x-ray* None of our patients showed improvement in their bony metastases, as determined by serial x-ray studies In fact, 6 actually had an increase in the number and size of metastases The others showed no real change

HORMONAL STUDIES

1 *17-Ketosteroid excretion* The excretion of 17-ketosteroids was followed in all of our patients Four of the 10 patients had a definite decrease in their urinary 17-ketosteroids In the others, all of whom had very low levels to begin with (below 2 mg /24 hrs) there was no change It is of interest that all but one patient had initial 17-ketosteroid levels of 1 1 mg /24 hrs or less, the exception having an initial level of 6 8 mg /24 hrs The relationship between changes in 17-ketosteroids and clinical improvement can be summarized as follows

Decrease in 17 ketosteroids and clinical improvement	4 cases
No change in 17 ketosteroids and clinical improvement	4 cases
No change in 17 ketosteroids and no clinical improvement	2 cases

2 *Protein bound iodine* Serial determinations of the protein-bound iodine as a measure of pituitary thyrotropic and thyroid function were done on 4 of our 10 patients All 4 showed a consistent and steady decrease from an average control level of 6 5 micrograms/100 cc to an average of 3 8 micrograms/100 cc This is consistent with reported results [13] [14]

3 *Pituitary gonadotropin excretion* (FSH + LH) The urinary excretion of gonadotropin was followed in 3 of the patients, with initial levels on 2 more In all 5, the reactions were initially zero The 3 patients which were followed had marked increases in gonadotropin excretion while on cortisone, their levels ranging between 80 and 220 M U /24 hrs This rise of gonadotropin during cortisone (and ACTH) therapy has been previously described during treatment of arthritis and other diseases [15]

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[13] Wolfson, W Q and others Corticogenic hypothyroidism, its regular occurrence and clinical significance during prolonged therapeutic administration of ACTH or cortisone J Lab & Clin Med , 36 1005–1006, 1950

[14] Hardy, J D Riegel, C and Erisman E P Experience with protein bound iodine (PBI), effect of ACTH 950

[15] Sohval, A R and on urinary gonadotropin c

TABLE 1

PATIENT AGE	GOOD RESPONSE TO ORCHIECTOMY	DATE CORTISONE STARTED AND DOSE PER DAY (mg.)	SYMPTOMATIC CHANGE (SUBJECTIVE AND OBJECTIVE)	CHANGE IN LOCAL PROSTATIC LESION	ACID PHOSPHATASE	ALKALINE PHOSPHATASE	X-RAY METASTASES	17 KETOSTEROIDS	IMPROVEMENT		LENGTH OF REMISSION
									Subjective	Objective	
GW* 59	x	3-30-52 100	No decrease in pain. Some increase in appetite. No weight change	Complete disappearance of palpable prostatic tissue—originally there was stony hard 2 cm. nodule.	Decreased 15 → 18 → 13 → 26 (KA)	Increased 20 → 37 → 55 → 73 → 96 (KA)	Increased	Low to begin (1.2 mg./24°) No change	0	x	None except local lesion and improvement in phosphatases. Bilateral adrenalectomy done
FC† 52	x	6-10-52 50 7-22-52 100 8-2-52 200 11-1-52 150	Complete relief of severe pain for 1 month with marked increase of appetite & 12 lb. weight gain. Then mild intermittent pain for 1-2 days every 2 weeks. Improved urination	Complete disappearance of palpable prostatic tissue—was originally large, stony and nodular. After 5½ months began to reappear	Increased after 3 months, 1 → 6 → 11 → 22 (B)	Increased 6 → 11 → 13 → 15 (B)	Increased	Definite fall (1.1 → 1 mg./24°)	x	x	Six months. Bilateral adrenalectomy then done
ML 77	x	8-8-52 50	Tremendous improvement in strength, appetite. Loss of pain. 10 lb. weight gain, ability to walk, increase of urinary stream.	Softening and shrinking of nodules. (At post, gland very small and soft.)	Slight increase 1 → 5 (B)	Decrease, then same 22 → 10 → 20 (B)	No change	Down (3.9 → 2 mg./24°)	x	x	Ten weeks. Died 10-26-52, bronchopneumonia
RS 76	x	8-3-52 50	Complete loss of pain in back and legs, allowing him to walk miles each day. Tremendous improvement in appetite—before severe anorexia. Weight gain 17 lb. in 6 wks.	Softening of gland with disappearance of nodularity. Smaller. Marked improvement in urination. Residual from 300 cc. to less than 80 cc.			Increased	Low to begin with (1.9 mg./24°). No change	x	x	Three months
GD 62	x	10-4-52 50 10-18-52 75	Increased appetite, decreased pain, increased strength. Able to get out of bed where before	No change	Increased then decreased, then slight increase	No change 11 → 20 → 21 → 18 (KA)	Increased in size. Collapsed vertebrae	Low to begin with (2.0 mg./24°). No change	x	0	2½ weeks

			He could not Decreased swelling of legs by measurement All very transient Collapsed vertebrae—paraplegia after 2½ weeks		18 → 50 → 12 → 32 (KA)						
HM† 55	x	8 18 52 50 10-9 52 100	Complete disappearance of pain, increase of strength and appetite	No change	Slight increase 0 8 → 2 6 (B)	No change 2 5 → 2 0 (B)	Increased (Developed path fracture of pubic ramus)	Not done Were 3 1 mg /24° before adrenalectomy	x	0	8 weeks Bilateral adrenalectomy done
BS 79	0	11-18 52 50 1 22 52 100	No change—only mild pain to begin with No improvement in weight or appetite or sense of well being	No change	Essentially unchanged 6 5 → 5 9 (KA)	No change 10 5 → 11 (KA)	No change	Low to begin with (1 0 mg /24°) No change	0	0	No remission
GN 67	x	11 24 52 50 1 14 53 100	Disappearance of severe pain & stiffness No longer required pain medication Able to walk well climb up & down—before had to lift rt leg with hands Increased appetite & strength Gained 10 lbs	Complete disappearance of three fixed stony nodules Two returned after four months	Increased 7 → 11 → 17 (B)	No change 7 → 9 → 8 (B)	Progression	Decreased (6 8 → 1 9 mg /24°)	x	x	4½ months
WC 77	0	11-22-52 50 1 14 53 100	Some decrease in difficulty of urination Nocturia from 7 8X to 3X residual from 300 cc to 90 cc Disappearance of back pain Increased appetite	Shrinking of gland from 3+ to 1+ with loss of nodularity and marked softening After 3 months begin to increase in size	Decreased 7 → 1 (B)	No change 5 → 7 (B)	No change	1 0 No change	x	x	4 months
RB‡ 64	x	2 20-53 50	Marked increase in strength sense of well being appetite Loss of nausea and vomiting	No change	Decreased 22 → 8	Not done	Progression	Decreased (2 4 → 1 8)	x	x	3 months (Still doing well)

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* Referred by Dr Frederick S Howard

† Referred by Dr Miley B Wesson

‡ Referred by Dr Sidney Olsen

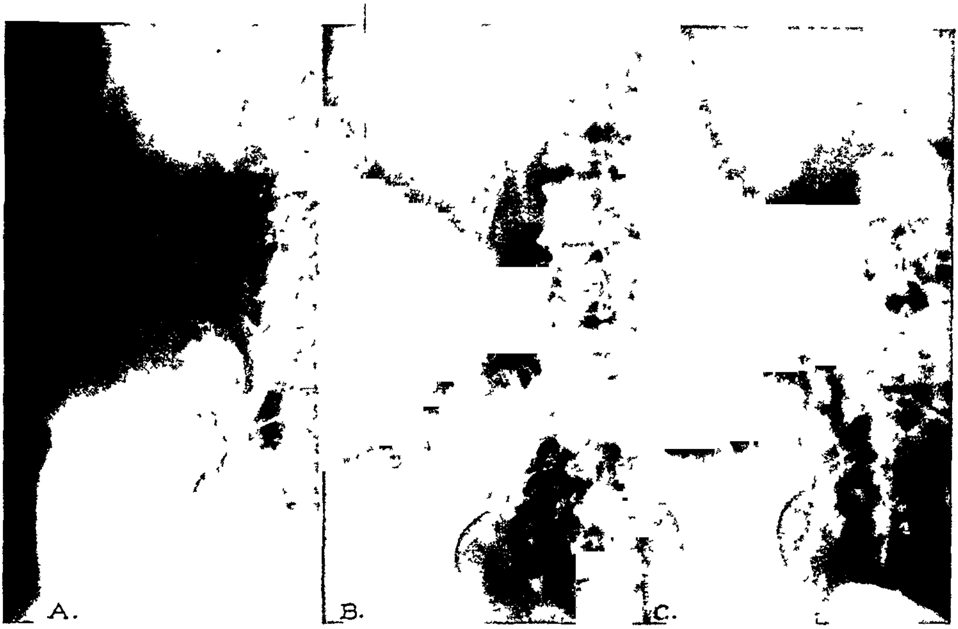

FIG. 1. *A*, excretory urogram showing hydronephrosis, secondary to ureteral involvement by prostatic carcinoma. *B*, after remission on cortisone therapy, showing regression of dilatation *C*, after relapse.

4. 17-Hydroxy-corticoid excretion (*compound F*). The urinary excretion of compound F was studied in 5 of the patients. The initial levels averaged 13 mg./24 hrs. and all were considered within the normal range. Following the administration of cortisone they all had the expected increase in 17-hydroxy-corticoid excretion.

COMPLICATIONS

The only complication from cortisone therapy encountered in our series was the reactivation of an old ulcer in one patient. His symptoms responded to extensive medical therapy despite the continuation of cortisone. No hemorrhage or perforation occurred, although this danger should be kept in mind. Therefore, it would be unwise to treat a patient with a known active or recently active ulcer with cortisone.

All of our patients were placed on a low sodium diet to prevent the possible occurrence of edema from the sodium retention action of cortisone. Those who did not have frank cardiac disease were placed on a diet containing 1 gm./24 hrs. of sodium, and the others on 300 mg./day. The patients on 50 mg. cortisone a day were given 3 gm. of potassium chloride (tablets) by mouth each day. When the cortisone dose was raised to 100 mg./day, the potassium chloride was increased to 6 gm. in divided doses. If stilbestrol should be given along with cortisone, then the dangers of salt retention and subsequent edema would be much increased. Frequent injections of a mercurial diuretic might then be necessary.

No difficulty with hypertension was encountered. One patient was a mild diabetic but no adverse effects were noted.

The dangers of sudden withdrawal of cortisone after a prolonged course are

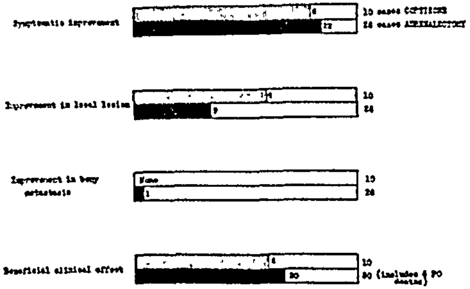

Fig. 2. Cortisone and bilateral adrenalectomy: comparative results (adrenalectomy figures are from the combined series of Huggins and Bergenstal,[3] West et al.[16] Harrison et al.[11] and Leberman et al.[17])

real inasmuch as such patients would be temporarily in a state of adrenal insufficiency. By gradual withdrawal, this complication can be avoided.

THE NUMBER OF PATIENTS OBTAINING REMISSION AND THE LENGTH OF THIS REMISSION

We feel that 8 out of the 10 patients had a clinical remission on cortisone therapy and in 6 out of these 8 there was some evidence of tumor regression by change in the local prostatic lesion or acid phosphatase decrease.

However, the length of the remission was relatively short and varied from 17 to 180 days with an average of 82 days.

COMPARISON WITH PUBLISHED CASES OF BILATERAL ADRENALECTOMY

Since we have attempted by means of large doses of cortisone to produce a "medical adrenalectomy," a comparison of our results with the effects of surgical bilateral adrenalectomy is important. We have drawn on the published results of four series, those of Huggins[3] (University of Chicago), West[16] (Memorial Hospital, New York), Harrison[11] (Peter Bent Brigham Hospital), and Leberman[17] (University of Pennsylvania). Together these give a total of 26 patients available for analysis, omitting 4 additional patients who died in the immediately postoperative period (fig. 2).

1. Symptomatic improvement. Twenty-two out of the 26 patients had symptomatic improvement. Again, here as in our cortisone series, the most striking thing noted was the relief of severe and often crippling bone pain.

2. Improvement in local prostatic lesion. Nine out of the 26 patients were noted to have marked decrease in the size of their local pelvic lesions.

3. Acid and alkaline phosphatase. Six of the 26 patients had a consistent decrease in acid phosphatase following adrenalectomy. Alkaline phosphatase data are difficult to interpret.

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[16] West, C. D., Hollander, V. P., Whitmore, W. F., Jr., Randall, H. T. and Pearson, O. H.: The effect of bilateral adrenalectomy upon neoplastic disease in man. Cancer, 5: 1009–1018, 1952.

[17] Leberman, P.: Bilateral adrenalectomy in prostatic carcinoma. (In press.)

4. Changes in bony metastases by x-ray. As was seen in the cortisone series, 18 out of 20 showed a steady progression of metastases. One patient of Harrison had definite improvement in the metastatic lesions and one in the Memorial Hospital series perhaps had temporary arrest.

5. Number of patients with remission and length of remission. Twenty of the 26 patients surviving bilateral adrenalectomy (omitting 4 additional patients dying postoperatively) were felt to have clinical remissions.

The period of improvement in the Memorial Hospital series varied from 14 to 220 days, averaging 83 days. This is almost identical to the average length of remission in our cortisone series (82 days). However, the average length of remission in the other adrenalectomy series appears to be considerably longer.

EFFECTS OF BILATERAL ADRENALECTOMY AFTER CORTISONE IS NO LONGER EFFECTIVE

We performed late bilateral adrenalectomy on 3 of our 10 patients. Two were operated on after exacerbation occurred following good remission from cortisone alone. One of these (H.M.) had beneficial symptomatic effect from cortisone for two months without improvement in local lesion or metastases. Adrenalectomy was performed 2 months after cortisone was discontinued. At present, 6 months after operation, he is back working hard on his cattle ranch and is asymptomatic, whereas before he was bedridden. His acid phosphatase excretion decreased from a preoperative level of 4 Bodansky units to 1 unit after one month and 2 units after eight months. A large metastatic lesion in the right inguinal region which was extremely tender and painful immediately became no longer painful but only started to decrease in size during the past month, along with marked shrinking of his local prostatic lesion. It may be of some significance that in the last 6 weeks his maintenance dose of cortisone was increased from 37.5 mg. to 75 mg. per day. He has had an excellent clinical remission.

The second patient (F.C.) was completely relieved of his severe pain for four weeks after operation but then began having pain as severe as before. It is now 5 months since operation. He requires 75–100 mg. of cortisone a day to prevent adrenal insufficiency. No improvement is noted in his local lesion and there has been progression of the metastases. His acid phosphatase decreased from 22 Bodansky units to 6 units after four weeks but now is 13 units. No change occurred in alkaline phosphatase excretion.

The third patient (G.W.) was operated upon after a month of cortisone therapy had failed to produce any symptomatic relief or alter his progressive downhill course, although it caused his local lesion to disappear by rectal palpation. Adrenalectomy gave him marked symptomatic improvement which, however, lasted less than eight weeks. During this period, his acid phosphatase excretion which had fallen from 45 King Armstrong units to 26 units on cortisone, rose progressively to 82 units. His alkaline phosphatase, which had risen from 29 units to 96 units, fell progressively to 50 units. He died from his malignant disease eight weeks after surgery.

DISCUSSION

The basis for endocrine therapy in carcinoma of the prostate stems from Huggins' initial work[18, 19, 20] with bilateral orchiectomy and estrogen therapy. From this he postulated that prostatic cancer represents an overgrowth of adult prostatic epithelial cells and like these cells, it undergoes atrophy when the androgens are reduced. Prostatic carcinoma is therefore dependent on the presence of circulating androgen for its growth. Castration or testicular inhibition by decrease of the pituitary gonadotropin output by estrogen results in a decrease in androgen which in turn prodces a decrease in the size of the tumor and in the function of the cancer cells.

After orchiectomy there is a fall in 17-ketosteroid excretion, followed by an increase for prolonged periods [Scott and Vermeulen[21]]. The preliminary fall is due to removal of the gonads. Increased extragonadal production of androgens presumably in the adrenal glands might account for later relapse after orchiectomy. Enlargement of the adrenals has been described in patients no longer responding to anti-androgen therapy. The mechanism for this increased adrenal androgen production for a long time was thought to be by stimulation of the increased pituitary gonadotropin which results from castration. This theory has now been questioned and the exact mechanism is still uncertain.

Huggins feels that cancer of the prostate eventually becomes autonomous, that is independent of androgen, and is no longer repressed by anti-androgenic therapy. Total failure of castration and estrogen therapy in approximately 20 per cent of the patients could then be explained on the basis of primary androgen independence. Support of this theory comes from Deming's work[22] on intraocular tissue transplants in which it was found that after passage through 8 male generations, the tissue then became independent of androgen and was able to grow in an estrogenized animal.

In the last few years, attempts have been made to diminish androgen secretion by the suppression of the pituitary gland by hormones other than estrogens. Trunnell et al.[23] used progesterone in the treatment of patients with advanced prostatic carcinoma on the basis of Albright's theory[24] that androgen production

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[18] Huggins, C. and Hodges, C. V.: Studies on prostatic cancer; the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Research, 1: 293-297, 1941.

[19] Huggins, C., Stevens, R. E., Jr. and Hodges, C. V.: Studies on prostatic cancer; the effects of castration on advanced carcinoma of the prostate gland. Arch. Surg., *43: 209-223*, 1941.

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[22] Deming [illegible] hormonal factor in heterologous growths of human [illegible] 948.

[23] Tr [illegible] V., Whitmore, W. F. and Woodard, H. G.: The use of progesterone in treatment of cancer of the prostate. J. Clin. Endocrin., 11: 663-676, 1951.

[24] Albright, F. and Elrick, H.: An attempt to classify hormonal disorders of the hypophysis. Tr. A. Am. Physicians, 61: 42-53, 1948.

depended on the secretion of luteinizing hormone (LH). They had excellent results in 8 of 10 patients that had had no previous therapy and in 3 of 6 patients who were in relapse after the usual hormonal therapy. However, some doubt has been cast on the LH theory as the major mechanism, since 17-ketosteroids increase after ACTH administration. As has been shown, the 17-ketosteroid excretion will decrease with inhibition of ACTH by cortisone.

Although the evidence for the importance of androgens in cancer of the prostate is sound, it does not extend to their exact role in the induction of the cancer or in the maintenance of its growth. Questions arise because of the well established fact that the average testis produces less androgen and more estrogen as age advances and yet cancer of the prostate is principally a disease of the elderly male. Moreover, studies on average 17-ketosteroid levels in these patients as compared with other males in the same age group showed no essential difference. The possibility thus occurred to us that there might be basic metabolic differences in these patients so that their androgens were not primarily secreted as 17-ketosteroids which would explain the dilemma. However, our few experiments[25] with exogenous androgen would indicate that this hypothesis was wrong since 2 untreated patients with prostatic carcinoma had the same rise in urinary 17-ketosteroids after a test dose of 100 mgm. of testosterone propionate as a young and an old normal patient. However, they don't completely rule out the possibility of abnormal metabolism of endogenous, as opposed to exogenous, androgen. Brendler and Scott[26] used large doses of testosterone on 3 patients with advanced disease. Two showed general improvement for a while, similar to the patients treated by cortisone or adrenalectomy and yet their acid phosphatases rose and the disease progressed—a non-specific effect of the steroid similar to that we have seen with cortisone.

Bilateral adrenalectomy was undertaken by Huggins because of experimental evidence on the role of the adrenals in neoplasia[27, 28] and in cancer of the prostate in particular, to remove the extra-gonadal source of androgen. This surgery has been successful only in carcinoma of the breast and carcinoma of the prostate, both of which are tumors felt to be under some endocrine control.

That the use of rather large suppressive doses of cortisone alone (in advanced carcinoma of the prostate) gives results similar to surgical bilateral adrenalectomy is not surprising when one considers that essentially what we have done is to produce a "medical adrenalectomy." This is analogous to the use of estrogen alone in place of orchiectomy. Most of the symptomatic improvement seen in our patients on cortisone can be explained on the basis of the nonspecific effect of the drug and most of these effects can be seen in other diseases treated with cortisone. Because of this, one of our colleagues has aptly called cortisone the

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[25] Miller, G. M.: (Unpublished data.)

[26] Brendler, H., Chase, W. E. and Scott, W. W.: Prostatic cancer; further investigation of hormonal relationships. Arch. Surg., 61: 433–440, 1950.

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"magnificent aspirin." However, this is essentially the same symptomatic improvement as seen in patients after adrenalectomy, who of course are maintained on cortisone.

A point of confusion and a cause for speculation is the apparent improvement in the local prostatic lesion in a fair number of our own patients, and in the adrenalectomy patients as well, accompanied by occasional improvement in acid phosphatase, and yet with progression of bony metastases in most of the patients. One possible explanation is that the local lesion may be less undifferentiated and thus more susceptible to hormonal influence than the metastases.

Other mechanisms can only be mentioned here. From our findings and others[29] on the decreased thyroid function with cortisone administration, the possibility that the resulting decrease in general metabolism will also affect the metabolism of the tumor cells also exists but this does not explain the difference between the local lesion and the metastases. The question of inhibition of thyrotropic hormone as well as ACTH by cortisone arises.[30] Still another explanation of the shrinking of the prostate with cortisone arises from the known inhibiting effect of the drug on inflammatory tissue and thus the apparent shrinking of the tumor may be merely a decrease in the fibrous stroma. It must be considered that in cases no longer responding to one type of hormonal treatment, the residual tumor cells may have adapted themselves to become dependent on the new environment created by the treatment. This could explain the return of the local lesion in our two patients under these circumstances. However, Nathanson[31] contends the tumor may have acquired vulnerability to effective therapy with other hormones. Hence, it appears that a shift in the endocrine status, as by cortisone, of the host may affect the response of a given tumor to hormonal agents. Somehow not now apparent cortisone changes the cellular environment or intrinsic cellular processes, but in a way which is peculiar to each neoplasm or group of neoplasms.[32]

SUMMARY

Ten patients with disseminated carcinoma of the prostate in severe exacerbation following previous remission from orchiectomy and estrogen therapy were treated with cortisone, starting with 50 mg. per day by mouth in divided doses. Eight out of the 10 patients had marked subjective improvement and 6 out of the 10 had objective improvement with decrease in the size of the local lesion and in 2, decrease in acid phosphatase. These results are comparable to those reported after bilateral adrenalectomy. The duration of beneficial response was rather short, averaging 82 days. This is probably shorter than after surgical adrenalectomy. Hormonal studies were done and their significance to our knowledge of hormonal interrelationships in carcinoma of the prostate is discussed.

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CONCLUSIONS

When orchiectomy and estrogen therapy have failed in patients with advanced prostatic carcinoma, cortisone treatment will often give an additional remission.

Adrenal suppression by cortisone gives clinical effects similar to bilateral adrenalectomy in these patients. With either treatment, the effects are temporary but are of somewhat shorter duration with cortisone alone.

Bilateral adrenalectomy after cortisone has become ineffective still gives additional relief to the patients.

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TACE IN PROSTATIC CANCER: CLINICAL AND BIOCHEMICAL CONSIDERATIONS

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Tremendous strides have been made in the treatment of prostatic cancer since Huggins[1] developed the concept that androgen was capable of activating tumor growth in this condition, and that inhibiton of androgen production or action by orchiectomy or estrogen administration often resulted in reduced activity of the neoplasm.[1, 2] The initial improvement which resulted from orchiectomy and estrogen administration in many cases has been followed by exacerbation of the tumor, and this occurrence has led Huggins[3] to suggest that androgen from an extragonadal source, the adrenal, was responsible.

It is well known that the administration of estrogens results in inhibition of the pituitary gonadotrophins so that the production of testicular androgens is markedly diminished.[4, 5] A further result of estrogen administration may be the neutralization of testicular and adrenal androgen before or at the prostatic tissue.[6] Recent evidence,[7] however, indicates that these beneficial effects of estrogen may be minimized due to the fact that estrogens themselves may be responsible for increased corticotrophin production. Whether the administration of estrogen actually results in increased adrenal androgen production is not known with certainty, but Harrison[8] considers this a distinct possibility, especially where excessively large doses of estrogen are used.

TACE,* a new synthetic estrogen, differs from other synthetic and natural estrogens in that it produces little or not adrenal hyperplasia in female rats[9] or in male rats.[10] A further difference is evidenced by the fact that in laboratory animals its administration does not produce pituitary enlargement.[9, 11]

On the basis of these differences and in view of the probability that TACE would not cause adrenal stimulation in man, we have administered it during the past 32 months to a series of 42 patients suffering from prostatic cancer. These patients were between the ages of 50 and 90, and the disease presented wide variations. Five patients had demonstrable metastases on admission, but the

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[1] Huggins, C. an Hoddges, C. V.: Cancer Res., 1: 293–297, 1941.

[2] Herbst, W. P.: J.A.M.A. 120: 1116–1120, 1942; Urol. & Cutan. Rev., 46: 691–694, 1942.

[3] Huggins, C. and Scott, W. W.: Ann. Surg., 122: 1031–1041, 1946.

[4] Heckel, N. J.: Clinics, 5: 860–877, 1946.

[5] Moore, C. R. and Price, D.: Am. J. Anat., 50: 13–72, 1932.

[6] Huggins, C. and Clark, P. J.: J. Exp. Med., 72: 747–762, 1940.

[7] Tepperman, J. and Tepperman, H. M.: Ann. Rev. Physiol., 12: 503, 1950.

[8] Harrison, J. H. and Poutasse, E. F.: Am. J. Med., 11: 55–66, 1951.

* TACE is the trade-mark of the Wm. S. Merrell Company, Cincinnati, Ohio, for its brand of chlorotrianisene (tri-p-anisylchloroethylene).

[9] Thompson, C. R. and Werner, H. W.: Proc. Soc. Exper. Biol. and Med., 77: 494–497, 1951.

[10] Trunnell, J. B.: Effect of TACE in the male rat. Read at TACE symposium, Cincinnati, Ohio, January 17, 1952.

[11] Shipley, E. G. and Meyer, R. K.: Some biological effects of TACE in animals. Ibid.

acid phosphatase was elevated in 9. Alkaline phosphatase was above normal in only 2 patients. Five patients had occult carcinoma. Twenty of the patients have had orchiectomy.

Estrogenic treatment was begun immediately following the diagnosis. Twenty-eight patients have received only TACE and the others who had received other estrogens previously were given TACE when it first became available. The usual dose of TACE was 24 mg. per day, but in some instances as much as 180 mg. were given daily. Nine of the patients were given TACE for 2½ years, 10 patients for 2 years, 6 patients for 1½ years, and 4 patients for slightly more than one year.

Twenty-nine patients in this series are still living and show definite improvement and a general well-being with normal phosphatase values and are free from metastatic lesions.

The following are instances of marked improvement when TACE was substituted for other estrogens:

Mr. J. R. M. had a transurethral resection in December 1948 and received 5.0 mg. of stilbestrol daily by mouth and 5.0 mg. weekly intramuscularly. Metastatic lesions of the lumbar spine and pelvis became progressively worse. TACE was begun in April 1951 and his condition improved remarkably. There was an increase in weight, his appetite improved, the blood phosphatase became normal, and the metastatic lesions disappeared. The improvement continued for 8 months, but the prostatic disease recurred and the patient died 6 months later.

Mr. H. A., aged 59, underwent transurethral resection for adenocarcinoma with metastases in April 1949. He received ethinylestradiol until December 1950 at which time he began to lose weight and suffered from pain radiating down the legs. Pelvic metastases were evident and the acid phosphatase was slightly elevated. Ethinylestradiol was discontinued and TACE was administered in a daily dose of 24 mg. At the present time, nearly 3 years after TACE therapy was begun, the patient is in excellent health with no local regrowth of tissue and no evidence of metastatic lesions.

Thirteen patients have succumbed during the study: Five of the deaths were attributed to cardiac disease. Nine of these patients had received other estrogens before TACE was administered and 4 had had only TACE. Seven of these 13 patients had survived for four or more years. At autopsy, the adrenal gland was normal microscopically and macroscopically in five patients who had received TACE for varying periods just before their death.

The estrogenic substances other than TACE caused nausea in 6 patients, vomiting in 3 patients, edema of the extremities in 3 patients, and some tenderness of the breasts in all cases. It is interesting to note that after discontinuing the other estrogens because of these side-effects, TACE was given and all symptoms disappeared. No patient has ever had sufficient gastro-intestinal upset, edema, or mastalgia while taking TACE to warrant its withdrawal.

In view of the important role which androgens play in prostatic cancer, 17-ketosteroid determinations were carried out on a number of patients. Human urine contains steroids which have ketone oxygen at C.17. Some of these steroids

TABLE 1. *Ketosteroid levels in normal men*

AGE GROUP	KETOSTEROID EXCRETION, MG./24 HOURS	REFERENCE
20–40	8–25	12
50–52	11.3	13
50–75	9.0	15
50–59	6.0	14
60–69	4.8	14
62–76	5.0	13
70–75	2.9	14
71–75	3.2–3.5	12

are phenolic while others are neutral. These latter are commonly called "17-ketosteroids." The principal members of this group are androsterone, etiocholanone, isoandrosterone and dihydroisoandrosterone. The first two of these arise in part from the testes, while all represent excretion products of some of the steroids of the adrenal cortex. Accordingly, the measurement of the 17-ketosteroid output provides a rough biochemical index of testicular and adrenocortical activity.

While the total neutral 17-ketosteroids levels in normal men between 20 and 40 years of age fall within the limits of 8 mg. to 25 mg. per twenty-four hours, the levels for older men are much lower.[12] In 5 normal men between the ages of 71 and 75 years, values of 3.2 mg. to 3.5 mg. were reported.[12] In 6 normal men whose ages ranged from 62 to 76, Frame and Jewett[13] found that the mean total 17-ketosteroid level was 5.0 mg. per 24 hours, while that for normal men between 50 and 52 was 11.3 mg. Hamilton and Hamilton[14] studied the effect of aging on ketosteroid excretion and found that in the age groups of 50 to 59, 60 to 69, and 70 to 75, the total ketosteroids excreted in 24 hours were 6.0 mg., 4.8 mg., and 2.9 mg., respectively. Kenigsberg[15] carried out 60 determinations on 18 normal men between the ages of 50 and 75 years, and found the group average to be 9.0 mg. per 24 hours with a range of 5 mg. to 15 mg.

In untreated prostatic cancer in men between 53 and 54, it was found that the total 17-ketosteroid excretion per 24 hours was 8.9 mg.[13] In an older age group, 62 to 76, the average value was 5.0 mg. with a range of 3.3 mg. to 6.8 mg. Scott and Vermeulen[16] found the precastration level in 10 men (47 to 80) with prostatic cancer to be 7.6 with a range of 3.6 to 11.7, while Satterthwaite, Hill and Packard[17] found the average value to be 5.2 mg. in a group of 14 patients with carcinoma of the prostate whose ages ranged from 54 to 83 years. The results of these investigations are summarized in tables 1 and 2.

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[12] Conference on ketosteroids, Josiah Macy Fund, 1942.

[13] Frame, E. G. and Jewett, H. J.: J. Urol., 52: 330, 1944.

[14] Hamilton, H. B. and Hamilton, J. B.: Aging in apparently normal men. I. Urinary titres of ketosteroids and of alpha-hydroxy and beta-hydroxy ketosteroids. J. Clin. Endocrin., 8: 433, 1948.

[15] Kenigsberg, Samuel, Pearson, Sidney and McGavack, T. H.: J. Clin. Endocrin., 9: 426, 1949.

[16] Scott, W. W. and Vermeulen, Cornelius: J. Clin. Endocrin., 2: 450, 1942.

[17] Satterthwaite, R. W., Hill, J. H. and Packard, E. F.: J. Urol., 46: 1149, 1941.

TABLE 2. *Ketosteroid levels in untreated prostatic carcinoma*

AGE GROUP	KETOSTEROID EXCRETION, MG./24 HOURS	REFERENCE
53–54	8.9	13
47–80	7.6	16
54–83	5.2	17
62–76	5.0	13

In view of the wide range that exists in the ketosteroid levels of young men, it is not surprising to find a similar variation in the aging male with and without prostatic cancer. While differences exist between the ketosteroid levels in the control groups and those with prostatic cancer it can be stated that no significant difference has been demonstrated. It is also apparent that there is fairly close agreement between the results of different investigators.

Following castration for prostatic cancer, Scott and Vermeulen[16] found that the average precastration levels of 7.6 dropped to a figure of 3.4 in an average period of 15.8 days following castration. There then followed a gradual rise to an average figure of 13.9 in an average period of 101 days and this figure then fell to 11.4 mg. at the end of an average period of 142 days. A similar study on an additional ten patients for a longer period showed that after an average period of thirteen months following castration, the ketosteroid level had dropped to 6.6 mg. per 24 hours, a figure not significantly different from those seen in the control group and in untreated cases of prostatic cancer.

Since considerable clinical improvement usually follows castration, much doubt is thus cast upon the validity of the widely held belief that low 17-ketosteroid levels must necessarily be present before clinical improvement is noted. This does not mean that androgens do not play an important part in the causation of prostatic cancer, as Huggins has claimed, but the results suggest that there may be no correlation between 17-ketosteroids determined chemically and androgens determined biologically. While it has been shown that there is a close agreement in some conditions between 17-ketosteroids and androgens,[18] these authors indicate that in liver disease and gynecomastia, the ratio of androgen to 17-ketosteroids is low. Not all 17-ketosteroids possess the same degree of androgenicity and it should be borne in mind that the terms, "androgen," and "17-ketosteroids," are not necessarily synonymous.[3] If high 17-ketosteroid levels, per se, were responsible for prostatic cancer, it is difficult to reconcile this with the fact that prostatic cancer is extremely uncommon in the younger age group in which 17-ketosteroid levels are characteristically high, and most common in the older group whose levels have been found to be low. We have not carried out determinations which would indicate a relationship between 17-ketosteroids and biological androgens in prostatic cancer, but it would seem that such a study would produce extremely valuable information.

In the present study, the total neutral 17-ketosteroid determinations were carried out on the urine of 19 patients who were suffering from prostatic cancer. All but 1 of these patients had received varying amounts of TACE prior to the

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[18] Zarrow, M. X., Munson, P. L. and Salter, W. T.: J. Clin. Endocrin., 10: 692, 1950.

TABLE 3. *Observations in 15 patients with prostatic carcinoma receiving* TACE (no orchiectomy)

	AGE	TACE STARTED	DAILY DOSE, 12 MG. CAPSULES	TOTAL CAPSULES	DAYS ON TACE	DATE OF K. S.	KETOSTEROIDS, MG./24 HRS.	ACID PHOSPHATASE	PRESENT STATUS	METASTASES
J. H.	60	1/ 3/51	2	654	327	11/26/51	11.0	5/50 .4 7/50 .3 2/51 .4	Good	none
H. N.	65	10/19/51	2	58	49	11/29/51	18.5	3.8	Good	none
F. T.	70	11/26/51	4	76	19	12/14/51	5.7	.02	Good	none
H. H.	55	1/13/51	2	664	317	11/26/51	21.6	11/51 2.8 11/52 2.7	Died 12/52	none
H. A.	60	12/26/50	2	678 1880	340 373 910	12/ 4/51 1/ 7/52 7/24/53	16.5 26.5 14.0	12/50 1.6 12/51 3.2	Good	none
J. R.	85	9/ 6/51	2	190	95	12/11/51	3.6	9/51 2.0 1/52 2.4	Died 8/52	none
J. J.	70	11/51	2	78	39	12/13/51	5.5	10/51 15.4 11/51 12.0 2/52 0.4	Died 4/53	none
F. P.	65	4/24/51	3	729	240	12/24/51	4.7	11/50 32.0 12/50 7.2 12/51 5.0	Fair	Yes
G. B.	63	7/ 1/51	3	513	171	12/21/51	9.8	7/51 .4 12/51 .3 3/52 .5 6/52 .1	Fair	none
J. J.	90	9/26/51	2	100	90	12/24/51 1/ 3/52	9.2 6.6	3.6	Good	none
E. P.	62	4/24/51	2-4	466	240	12/17/51	8.6	9/50 2.0 12/51 3.0	Good	none
J. R.	64	10/ 3/51	4	288	72	12/14/51	11.1	9/51 .4 12/51 .1	Good	none
C. S.	85	1/15/51	2	660	360	12/15/51	9.0	1/51 3.8 1/52 2.2	Good	none
J. M.	75	4/18/51	2	615	240	12/ 7/51	14.1	12/48 2.9 12/51 2.9	Died 8/52	yes
E. M.	70	1/ 6/51	2	720	365	1/52	6.8	1/52 1.8	Good	none

TABLE 4. *Observations in 3 orchiectomized patients with prostatic carcinoma receiving* TACE

	AGE	TACE STARTED	DAILY DOSE, 12 MG. CAPSULES	TOTAL NO. CAPS.	DAYS ON TACE	DATE OF ORCHIECTOMY	DATE OF K. S.	KETOSTEROIDS, MG./24 HRS.	ACID PHOSPHATASE	PRESENT STATUS	METASTASES
C. N.	70	1/ 1/51	2	626	270	10/51	11/26/51 1/ 4/52	5.9 17.7	9/49 1.8 11/51 3.4 1/52 4.6	Died 1/52	none
W. F.	57	7/15/51	2	270	150	7/51	12/ 3/51	7.0	12/51 2	Good	none
F. M.	80	8/13/51	2–15	1383	180	11/42	12/12/51 2/ 5/52	5.5 9.8	12/51 190 1/52 356	Died 2/52	yes

TABLE 5. *Observations in patients not suffering from cancer of the prostate*

	AGE	DATE OF KETOSTEROID DETERMINATIONS	KETOSTEROIDS, MG./24 HRS.
F. T.	70	11/26/51	14.8
A. S.	70	12/17/51	8.3

collection of the urine specimen. Orchiectomy had been performed on 3 patients before the ketosteroid determinations were done and after the determination in 1 case. Ketosteroid determinations were also carried out on the urine of 2 patients in a similar age group who did not have prostatic cancer. The method of Hawk[19] was used with slight modifications to make for accuracy with the spectrophotometer and a solution of dihydroandrosterone was used as a standard. The results are given in tables 3, 4, and 5.

In the 15 patients on whom orchiectomy had not been performed and who were receiving only TACE, the range of 17-ketosteroid excretion was 3.6 mg. to 26.5 mg. with an average of 11.3 mg./24 hours. This latter value is in close agreement with the findings of O'Conor and Sokol.[20]

The average value of the determinations in a group of patients who were orchiectomized and who have received TACE was 9.2 mg. This figure was not significantly different from that found in the preceding group (11.3 mg.) and also not significantly different from Scott's figure of 6.6 mg.

In our two control patients who do not have cancer and who received no TACE, the mean value was 11.5 mg., while one determination in a case of untreated prostatic cancer was 8.5 mg.

A relationship between high 17-ketosteroids and the clinical condition was not established in our study, but it must be stated that a sufficient number of determinations was not done to arrive at any conclusion other than to say that a wide variation in levels existed. Insofar as establishing a relationship between the clinical condition and 17-ketosteroid levels is concerned, it would be extremely difficult to establish this while the patient is receiving an estrogen because the factor of biological antagonism between estrogens and androgens must be considered. Our findings also indicate that there was no relationship between 17-ketosteroid levels and acid phosphatase determinations. The excretion of 17-ketosteroids appeared to be unaffected by the administration of TACE.

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[19] Hawk, P. B., Oser, B. L. and Summerson, W. H.: Practical Physiological Chemistry. Philadelphia: The Blakiston Co., 1948, p. 700, 12th ed.

[20] O'Conor, V. J. and Sokol, J. K.: Evaluation of TACE as a therapeutic agent in prostatic carcinoma. Read at TACE Symposium, Cincinnati, Ohio, January 17, 1952.

SUMMARY AND CONCLUSIONS

A series of 42 patients suffering from prostatic cancer has been treated by surgical methods and the new synthetic estrogen, TACE, during a period of 32 months.

TACE was well tolerated even when extremely large doses were administered and there was a virtual absence of undesirable side-effects.

In many patients in whom the disease had become resistant to other synthetic and natural estrogens the administration of TACE resulted in clinical improvement. This was characterized by an increase in weight, a decrease in pain, an improvement in the blood picture, and regression of metastatic lesions.

In five TACE-treated patients who came to autopsy there was no evidence of the adrenal hyperplasia which has been observed in laboratory animals following the administration of some other synthetic estrogens.

Sufficient time has not yet elapsed for us to compare the survival time in TACE-treated patients to that observed in patients treated with other synthetic or natural estrogens.

The urinary excretion of 17-ketosteroids was investigated in 21 patients who had received daily doses of 24 mg. to 180 mg. of TACE for many months and the findings indicate that the administration of TACE has no adverse effect upon adrenocortical function. The significance of 17-ketosteroids determinations in prostatic cancer is discussed.

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RESULTS OBTAINED BY ENDOCRINE CONTROL THERAPY FOLLOWED BY RADICAL PERINEAL PROSTATECTOMY IN TWENTY-FIVE SELECTED CASES OF ADVANCED CARCINOMA OF PROSTATE

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It was to be expected that the marked regression of the carcinomatous prostate which so frequently resulted from endocrine control therapy would suggest to a number of observers a broadened field of usefulness for the perineal prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate. Vallett in 1944 seems to have been the first to use this combined therapy on a case of this sort but unfortunately the patient died too soon after surgery to permit any conclusions as to its efficacy. Later in the same year Parlow and then Colston recommended its use in selected cases. In December of that year Scott and Benjamin reported 2 cases which had recently been treated in this manner. In 1947, Colston and Brendler reported one death within a year in 7 cases that had been followed 2 years after surgery. Parlow and Scott in 1949 reported their results in a series of 14 cases treated by this combined therapy. One year later Scott and Parlow reported that 22 cases had been treated by this method in their clinic and presented a detailed report on the first 13 cases, all of which were living and apparently well after the institution of therapy. Scott in 1953 presented a detailed report on 21 selected cases of advanced carcinoma of the prostate that had been treated by this method and which had been followed three years or more after treatment was started.

Inasmuch as any attempt to evaluate the efficacy of this combined therapy in the treatment of selected cases of advanced carcinoma of the prostate gland is necessarily influenced by the types of case included in such a study, it might be helpful if our determining selective factors were presented and discussed at this time. Obviously those patients, in whom, because of recent origin or latency of growth, the carcinoma, when first discovered, is so situated as to permit a reasonable chance for its complete removal by radical surgery, should not be included in this group. All patients with proven metastases when first seen, regardless of their response to hormone therapy, are not suitable candidates for the follow-up radical surgery. Radical surgery offers practically no hope of cure to the patients without metastases in whom the local growth is a little too extensive to permit its complete removal when first seen and who fail to respond to endocrine therapy. Where the local growth has advanced to such an extent as to result in the formation of a well-defined, intervesicular plateau when the patient is first seen, it is reasonable to assume that lymphatic and perineural extension beyond the palpable area may have occurred even though the presence of metastases cannot be proven. In such cases, regardless of a remarkable local response, it would seem that while a follow-up radical perineal prostatectomy

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might increase the patient's life expectancy and freedom from distressing urinary symptoms, it should still be considered of questionable value. In the presence of nodular intravesical extension beyond the bladder neck when the patient is first seen, the combined therapy seems to be contra-indicated. However when the aforementioned conditions have been excluded there still remains a very encouraging number of cases with carcinoma of the prostate from which the patients to be treated by the combined therapy can be selected.

These are the patients in the group of advanced carcinoma of the prostate without metastasis in whom the carcinomatous extension beyond the confines of the prostate, while not marked, is too great to permit its complete extirpation by radical surgery when the patient is examined. It is for the patients in this group, providing their response to hormone therapy has been such that a digital examination at the time of maximum regression suggests that complete extirpation of the carcinomatous lesion might be possible, that we believe a follow-up radical perineal prostatectomy offers a chance for a cure, or failing in this will at least prolong the patient's life and freedom from distressing symptoms. But even some of these patients have to be excluded because advanced age or their general physical condition seem to contra-indicate radical surgery.

It seems to us that the decision as to whether or not the patient is a suitable candidate for radical surgery is less difficult to make on the basis of his age than from the standpoint of his general physical condition. Because of their limited life expectancy and because carcinoma of the prostate is often a very slow process in patients who are 80 or more years of age, we have not used the combined therapy in any instance where the patient was that old when first seen. We have learned that as a result of careful preoperative and postoperative care, proper supportive measures during operation and the availability of very satisfactory antibiotics, the radical perineal prostatectomy, while sometimes requiring a little longer to perform, is seldom more disturbing to the patient than some of the more commonly used surgical procedures upon the prostate. At least three of our patients had a history of coronary disease with cardiographic evidence of damage and yet were no more disturbed by the operation than the average case. As a rule the operative risk due to the presence of general physical disability is little if any greater than that of the other open operations upon the prostate for the correction of prostatic obstruction.

Up to the present time in the urological clinic of the Strong Memorial Hospital, we have treated 31 patients by this combined therapy, 25 of whom have been followed 36 months or more since treatment was instituted. The remaining 6 patients have not been under treatment long enough to warrant an attempt to evaluate the efficacy of the therapy upon them.

Since 21 of the 25 cases that have been followed 3 years or more have been presented in detail in a very recent publication, it might be more profitable at this time to present and discuss in detail the 5 cases in our series in which death was due to local recurrence or metastasis. In all the patients treated by this method the clinical, serological and radiographic studies were negative for the presence of metastasis. Furthermore all blood studies and renal function tests were within normal limits at the time of operation.

CASE REPORTS

Case 1. C. D., S.M.H., 211137, aged 72 when first examined on November 1, 1943, gave a history of gradual diminution in size and force of his urinary stream, increasing frequency and terminal dribbling of 6 months' duration. There had been no loss of weight.

The findings on physical examination were normal for a man his age except for the prostate which was moderately enlarged in all dimensions; its median furrow and notch were shallow and its surface was moderately smooth but very hard. It was fixed in position and extension beyond the base to the region of the seminal vesicles for a short distance had occurred on each side (fig. 1, *A*). His residual urine was 15 cc and a punch biopsy study revealed adenocarcinoma of the prostate.

Following a bilateral orchiectomy, performed on November 22, 1943, regression which was slow and not marked except in the anteroposterior diameter of the gland, reached its maximum point on November 14, 1944 when a follow-up radical perineal prostatectomy was performed. At that time there still remained some induration extending for a short distance towards the seminal vesicle in each side (fig. 1, *B*).

Studies of sections from the surgical specimen showed a scattered collection of large epithelial cells with hyperchromic nuclei and abundant pale-staining cytoplasm. Some of the cells were arranged in acinar fashion, but for the most part, they appeared as solid cords invading the dense connective tissue and smooth muscle. Cancer cells were found in the fascial tissue surrounding the seminal vesicles. Sections of nerves showed tumor cells within their sheaths.

The patient's convalescence was satisfactory and when he was discharged from the hospital 23 days after operation he was voiding satisfactorily and his control was perfect.

Because of his poor response to bilateral orchiectomy the patient was not placed on our routine postoperative course of estrogen therapy until a recurrent nodule was discovered on rectal examination 56 months after prostatectomy (fig. 1, *C*). He was immediately started on stilbestrol therapy which was later supplemented by deep x-ray and local radium treatments. He died of carcinomatosis on May 26, 1950.

This case failed, in at least one respect, to meet our criteria for treatment by this combined therapy. The growth, which was well beyond the confines of the prostate in the region of the seminal vesicles when the patient was first seen,

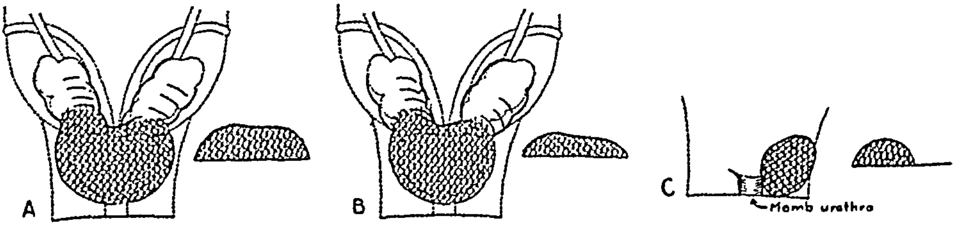

FIG. 1. *A*, prostate before castration November 11, 1943. *B*, only slight regression evident at time of radical perineal prostatectomy November 11, 1944. *C*, location and size of recurrence when first discovered on June 6, 1949.

responded but slightly to control therapy and therefore it is doubtful if a reasonable chance for its complete extirpation was present at the time of radical surgery. Inasmuch as during most of the 82 months that the patient lived following the institution of therapy he was quite comfortable and without urinary symptoms, it would seem that he derived some benefit from the treatment. We believe that we are now able to evaluate the surgical possibilities in cases of this sort much more accurately than at the time this patient was treated.

Case 2. O. J., S.M.H., 237491, aged 61 when first seen on September 17, 1943 complained of gradually increasing frequency, dysuria and dribbling of 3 years' duration.

He appeared to be in good physical condition but on rectal examination a prostate that was very hard and enlarged in all dimensions was found. There was extension of third degree induration beyond the base to the region of both seminal vesicles with beginning intervesicular plateau formation (fig. 2, *A*).

Stilbestrol therapy, 5 mg. a day, gave considerable relief of urinary symptoms but regression was slow so a bilateral orchiectomy was performed on April 5, 1945 and the estrogen therapy was continued. Within 4 months the involved area had regressed and softened markedly. It was firm but movable in spite of definite adhesions along its lateral margins (fig. 2,*B*). The radical perineal prostatectomy was performed on September 9, 1945.

On examination of the gross specimen an area of nodular hardness was found in the region of one seminal vesicle but there was no note that sections were taken from it. The tumor was of a diffuse infiltrating type. In some areas the connective tissue was studded with small acini, nests and cords of tumor cells. Many of the nests contained only 2–3 cells. Studies of sections from the periphery of the surgical specimen in a few instances showed cells in acinar form invading the nerve trunks.

The patient's convalescence was uneventful except that he had almost complete incontinence for a period of 2 weeks following the removal of his catheter. When discharged 28 days after operation his control was better but not perfect.

The patient was followed at regular intervals by the operator until June 10, 1947. At this time there was no evidence of local recurrence and urinary incontinence was only present on occasions of extreme physical fatique. Shortly afterwards he moved from Rochester leaving no forwarding address. A report to us that he was examined elsewhere on January 2, 1952 and found to be well was evidently unfounded. On April 27, 1953 we finally contacted his wife who in-

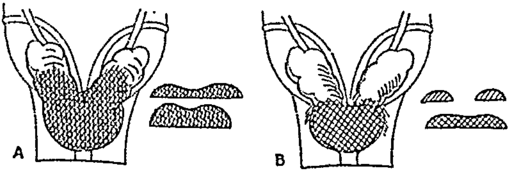

FIG. 2. *A*, prostate before stilbestrol therapy July 2, 1943. *B*, condition after supplementary orchiectomy July 17, 1945 and before radical prostatectomy September 9, 1945.

formed us that he died in Seattle of carcinomatosis on August 26, 1948 probably from a primary lesion of the prostate.

This case differed from the previous one in that the extension of the cancer to the region of the seminal vesicles was considerably greater and the regression due to control therapy was faster and more pronounced. The decision to perform a follow-up radical perineal prostatectomy in spite of very definite extension to the seminal vesicles with intervesicular plateau formation was greatly influenced by the marked response to control therapy. By so doing a criterion for the selection of patients for the combined therapy was violated. Although the patient was not cured the fact that he was quite comfortable during most of the 62 months he survived after treatment was started, suggests that he derived considerable benefit from it.

Case 3. B. F. C., S.M.H., 278670, aged 64 when first seen on April 14, 1948 complained of hesitancy, nocturia, recurrent hematuria and dysuria although a suprapubic prostatectomy had been performed elsewhere 3 years previously. His prostate was at least twice normal in size and the median furrow and notch were shallow. The lateral lobes were smooth but firm, being of second degree induration except at their bases where third degree induration was present, especially on the left side (fig. 3, *A*). As a result of this examination the clinical impression was benign prostatic hypertrophy plus inflammatory reaction. However on cystoscopic examination an irregular, bleeding, suspicious area was seen in the bladder just inside the vesical neck at about 4 o'clock. A diagnosis of adenocarcinoma probably of prostate was made from sections of this area. Treatment was complicated by the presence of moderately severe diabetes.

A bilateral orchiectomy performed on June 12, 1948 was supplemented by estinyl therapy, 0.05 mg. three times a day. By March 11, 1949 the right lobe of prostate had softened and regressed almost to normal size. Although the left lobe had decreased considerably in size, there remained a nodule of third degree induration covering a small area in the region of the base of the seminal vesicle (fig. 3, *B*). Since all studies were negative for metastases and on cystoscopic examination the area in the bladder had disappeared, a radical perineal prostatectomy was performed on March 15, 1949. A liberal cuff of the vesical neck was removed with the prostate and seminal vesicles. Pathological studies from prostate revealed carcinoma showing marked estrogen effect. The patient had good urinary control when discharged on estinyl therapy on April 4, 1949.

It would seem that although repeated blood phosphatase and radiographic

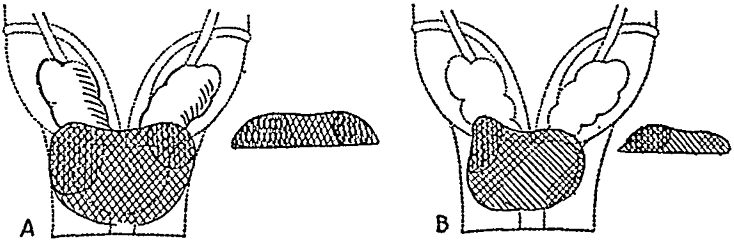

FIG. 3. *A*, situation at start of combined endocrine therapy June 12, 1948. *B*, condition at time of radical perineal prostatectomy March 15, 1949.

studies had been negative, metastasis had occurred before the radical prostatectomy was performed. Although at no time was there any evidence of a local recurrence, bone lesions were present within a year. The patient died of carcinomatosis on October 7, 1950. It now seems to us that the follow-up radical perineal prostatectomy is of very questionable value in those cases where extension beyond the vesical neck to the region of the trigone is present when the patient is first examined.

Case 4. G. O. B., S.M.H., 283183, aged 68, complained at the time of his first visit on September 20, 1948 of a gradually increasing frequency, nocturia, urgency and dribbling of 3 months' duration. The prostate was of third degree induration and greatly enlarged in its lateral and anteroposterior directions. Except for three very hard, discrete, nodular areas its posterior surface was relatively smooth. The median furrow and notch were absent. There was extension for a considerable distance up over each seminal vesicle with intervesicular plateau formation (fig. 4, *A*).

Following a bilateral orchiectomy on September 25, 1948, the patient was sent home on stilbestrol therapy with instructions to return at monthly intervals for observation. On March 14, 1949 the prostate had decreased to almost normal size and was of first degree induration. Second degree induration was present over the base of each seminal vesicle, more on the left than right, and between them there remained a plateau-like ridge of second degree induration (fig. 4, *B*).

A radical perineal prostatectomy was performed on March 17, 1949. The operator encountered marked difficulty in freeing the left seminal vesicle due to the presence of scar or carcinomatous tissue, probably the latter. He felt that extension beyond the operative field had occurred.

Active areas of carcinoma were found in sections from the prostatic and seminal vesicle portions of the surgical specimen. At the time of discharge, 30 days after operation, the patient occasionally dribbled slightly while at rest and considerably when under stress. Inasmuch as he was able to stop his stream completely during the act of voiding, we were confident that he would regain satisfactory control within a few weeks or months. Because of the relatively rapid progress of the disease the patient never returned for further observation. He died of carcinoma of the prostate on November 13, 1949.

In this patient at the time of operation there remained areas of second degree induration over the region formerly occupied by a well-defined intervesicular plateau due to extension from the prostatic carcinoma. In such cases the possi-

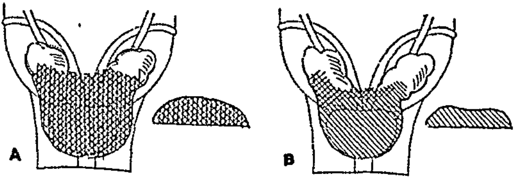

FIG. 4. *A*, prostatic involvement with extension to seminal vesicles when combined endocrine therapy was started September 9, 1948. *B*, induration due to cancer still present over seminal vesicles when radical perineal prostatectomy was performed March 14, 1949.

bilities of lymphatic and perineural extension or the presence of active tumor cells beyond the field of operation are such as to make the follow-up radical prostatectomy of very questionable value.

Case 5. V. M., S.M.H., 301085, aged 64 when first examined on August 29, 1949 complained of unusual fatique, decrease in size of stream, hesitancy and nocturia of 2 years' duration. Nothing of significance was found on physical examination except in the prostate gland which was moderately enlarged in all directions. Considerably more than half of the left lateral lobe was filled by a hard, irregular, fixed nodule that pushed its lateral border about 1.5 cm. beyond the confines of its normal contour and which extended medially almost to the median furrow (fig. 5, *A*).

Blood phosphatase and radiographic studies were negative for metastasis. Punch biopsy and Papanicolaou studies were positive for carcinoma.

The patient was placed on estinyl therapy 0.025 mg. three times a day and examined at monthly intervals until November 28, 1949. At that time the nodule seemed to have regressed sufficiently to permit its complete removal by radical surgery (fig. 5, *B*).

On cystoscopic examination the vesical neck simulated the picture of moderate collar hypertrophy. The residual urine was only 15 cc and there was no evidence of carcinoma extending into or beyond the vesical neck. On rectal palpation over the cystoscope an indurated nodule of moderate size was felt in the left lobe of prostate close to the apex. Although the outer border of the lobe was not well defined, the examiner thought there was a reasonable chance of getting around this area at operation.

On November 29, 1949 a radical perineal prostatectomy was performed. Considerable difficulty was encountered in developing a satisfactory line of cleavage between the lateral border of the left lobe of the prostate and the periprostatic tissue for a short distance just below the apex. However when this had been accomplished it appeared as though we had been able to get around the involved area.

His immediate postoperative course was very satisfactory. When he left the hospital 18 days after surgery his wound was healed and urinary control was good. He was sent home on estinyl 0.025 mg. daily, with instructions to return for a check on his condition at intervals of three months. A rectal examination on October 9, 1950 revealed a smooth operative field. His acid phosphatase was 5.1 and his alkaline 10.3 King-Armstrong units. On February 5, 1951 he returned

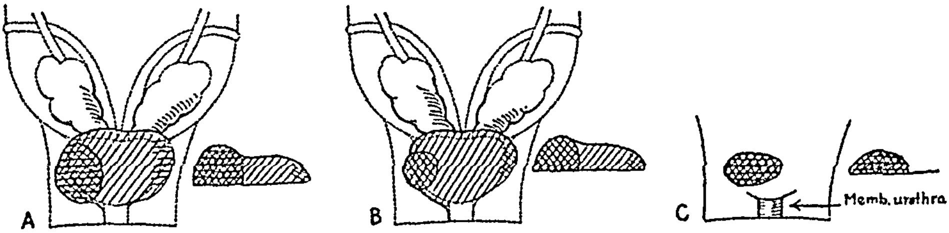

FIG. 5. *A*, extent of prostatic involvement when patient was first examined August 29, 1949. *B*, condition at time of radical perineal prostatectomy November 29, 1949. *C*, recurrence when first discovered February 5, 1951

with a story of increasing fatigue and pain along the course of the right sciatic nerve. A recurrent lesion was found that corresponded somewhat in size and position to the one which was present in the prostate at the time of his first examination (fig. 5, *C*). At this time his acid and alkaline phosphatase readings were 6.4 and 16.6 King-Armstrong units respectively. Radiographic studies were negative for metastasis.

The bilateral orchiectomy performed on February 6, 1951 was supplemented with estinyl therapy 0.05 mg. twice daily. The regression of the growth and the relief of pain were only temporary. In August 1951 the recurrence had increased in size and his right sacro-iliac and sciatic pain had become more severe. The pelvic mass shrunk to the size of a pea following 700 mg.-hr. of radium applied per rectum in fractional doses. On October 17, 1951, because the patient's pain was increasing and metastatic lesions were present, a course of deep x-ray therapy was started. The relief from this was quite temporary.

Because his symptoms, blood phosphatase, and radiographic studies indicated steady progress of the disease, the right adrenal was removed on February 7, 1952 and the left 11 days later. The disease continued to progress gradually and death occurred on August 8, 1952.

Judging from the pathological character and extent of growth in the surgical specimen there might have been a better chance for its complete extirpation had the preoperative treatment consisted of a bilateral orchiectomy in addition to the estinyl therapy and had it been prolonged up to the point of maximum regression of the carcinomatous lesion.

DISCUSSION AND RESULTS

Because in some cases of carcinoma of the prostate in which the response to endocrine therapy has been especially satisfactory it may be very difficult to demonstrate the presence of residual carcinoma by means of microscopical studies of sections from the surgical specimen, the operator who is unwilling to proceed with radical surgery without positive histopathological support should make these studies before starting treatment. In 19 of our cases the clinical impression of carcinoma was confirmed by biopsy studies made either before or very shortly after endocrine therapy had been instituted. In 3 cases carcinoma was found in the surgical specimen even though biopsy studies were negative. Pathological studies of a biopsy specimen obtained from the first patient in this series on his initial visit were typical of carcinoma of the prostate. Following castration and estrogen therapy the radical operation was performed 42 months later. A study of many sections from the surgical specimen repeatedly showed connective tissue formations very similar to those found in cancer of the prostate but the epithelial cells were either absent or so changed that a positive diagnosis could not be made. It is our belief that had a serial section of the whole surgical specimen been made, carcinoma cells would have been found. In 2 recent cases a clinical impression upon rectal examination by at least two of our senior staff, repeated positive Papanicolaou studies by a cytologist especially skilled in this particular field, and regression and softening of the suspected area following endocrine therapy, all pointed so strongly towards carcinoma that a radical perineal prostatectomy was performed.

Pathological studies of a considerable number of sections from each surgical specimen showed the pattern described above but no typical normal carcinoma cells were found. It is interesting that the cytologic studies in these cases showed progressive effect of the endocrine therapy upon the malignant cells which were very plentiful when the patients were first examined. In one case after 6 months of therapy, the malignant cells completely disappeared and remained absent until the radical operation was performed 2 months later. While the malignant cells did not completely disappear in the second case, they did decrease greatly in number and show marked estrogen effect before the operation.

In our opinion, all patients who have had a radical prostatectomy for cancer of the prostate gland should continue a routine course of some type of estrogenic therapy for a very long time after operation, regardless as to whether they were treated in the manner presented above or belonged to the more fortunate group, in which because of the size and location of the carcinomatous nodule, a preliminary course of endocrine therapy did not seem necessary. It is not always easy to convince some of these patients, who are feeling well and know that the organ which was the source of their trouble has been completely removed, that they must continue estrogen therapy even though at times it may cause some discomfort. However, the reasons for the postoperative continuance of estrogen therapy are so obvious and valid that even the most stubborn patient can be convinced of its necessity without creating a cancer phobia, if patience and discretion are exercised in their presentation.

When the clinical impression of carcinoma of the prostate has been definitely confirmed by a positive punch biopsy study in a patient who qualifies for the follow-up radical perineal prostatectomy providing the response to hormone control treatment proves to be successful, bilateral orchiectomy plus estrogen is the preoperative therapy of choice. As shown by Nesbit and Baum, the survival rate was better where these two types of endocrine therapy were combined than when either was used alone (table 1). Furthermore it seems to us that the cleavage lines are more easily developed and the whole operative procedure somewhat facilitated in the presence of a previous bilateral orchiectomy. Finally any lapse on the part of the patient with reference to his postoperative estrogen therapy might be covered, for a time at least, by the absence of the testicles.

The results of endocrine therapy plus a radical perineal prostatectomy in our first 25 cases have been most encouraging. In all these cases treatment was started 36 months or more before the material for this report was summarized. The longest time that had elapsed since endocrine therapy was started was 130 months, the shortest 14 months and the average time was 61.2 months. The average time after prostatectomy was 47.6 months, the longest 89 and the shortest 5 months. There were 4 deaths within 36 months from the time that the therapy was started. In one where carcinomatous tissue was left in the seminal vesicle region (case 4) the patient died of cancer 14 months after treatment was started and 5 months after surgery. Another patient died of coronary

TABLE 1. *Percentage survival at 6 month intervals of a series of 25 selected cases of advanced carcinoma of prostate without metastasis at time of first visit which were treated by endocrine therapy alone or combined with radical perineal prostatectomy as compared to a control series of similar cases (Nesbit and Plumb) treated by methods in use before introduction of endocrine therapy.*

TYPE OF THERAPY	MONTHS						NUMBER OF ELIGIBLE CASES	PER CENT DEAD NOT DUE TO CA.
	6	12	18	24	30	36		
Control (Nesbit and Plumb)....	72.0	54.0	39.0	32.0	25.0	20.0	273	—
Stilbestrol (Nesbit and Baum)..	90.7	82.2	75.6	69.1	56.2	49.7	143	34
Castration (Nesbit and Baum)..	91.6	84.9	74.0	65.9	62.2	53.4	239	26
Castration and Stilbestrol (Nesbit and Baum)...............	95.6	89.3	82.3	76.0	76.0	66.0	159	37
Endocrine therapy plus the radical perineal prostatectomy (Scott)......................	100	100	92.0	88.0	84.0	84.0	25	25
Total cases..................							839	

thrombosis 14 months after therapy was instituted and 8 months after prostatectomy. A very careful autopsy study revealed neither local recurrence nor metastasis. In the third patient (case 3) who died of metastases 28 months after the start of treatment and 18 months after his radical operation there was no evidence of local recurrence. The fourth patient who developed a reccurent lesion with metastasis was not greatly benefited by bilateral orchiectomy, deep x-ray therapy and bilateral adrenalectomy, dying of carcinomatosis 35 months after therapy was started.

Of the patients who survived 3 years or more after treatment was started 5 are known to be dead. There were two deaths due to recurrent and metastatic carcinoma from the prostate. One of these patients who died 82 months after start of therapy was not placed on estrogen therapy until a local recurrence was discovered 56 months after his prostatectomy (case 1, C). The other patient died of generalized carcinomatosis 62 months after he was placed on treatment. A third patient died of a primary carcinoma of the stomach 64 months after treatment was instituted while the fourth died of coronary disease 58 months after therapy was started. A fatal airplane accident 47 months after start of therapy resulted in the death of the fifth patient. In another patient who refused to take postoperative estrogen therapy and in whom a small, local, recurrent nodule was suspected 46 months after treatment was started, the area completely disappeared following orchiectomy and needle radiation therapy. When last seen 10 months later all studies were negative for cancer. Of the remaining 6 patients who have been followed less than 36 months one has developed a local recurrence and metastases.

Before attempting to evaluate the relative effectiveness of endocrine therapy plus the follow-up radical perineal prostatectomy in the treatment of carcinoma of the prostate, it seems advisable to emphasize that its field of usefulness is definitely restricted. It is our belief that in early carcinoma of the prostate where the lesion is contained within the confines of the prostate, the radical removal of the gland, seminal vesicles along with their posterior fascial covering should be accomplished as soon as possible after the diagnosis has been made. As pointed out previously the patients for whom the combined therapy offers the most hope are very carefully selected from the group of advanced carcinoma of the prostate who were without metastasis when first seen.

Fortunately, there is now available sufficient reliable data to permit a very satisfactory evaluation of the relative effectiveness of the various types of therapy used in the treatment of patients with advanced carcinoma of the prostate who were without metastasis when first seen. As a control series we have the report by Nesbit and Plumb on the survival rate at 6 month intervals on 273 of these cases which were treated by the methods in use before the introduction of endocrine therapy and followed for 36 months after their first visit. Based upon case material supplied by members of the Urosurgical Society, Nesbit and Baum in 1952 reported the survival rate at 6 month intervals for 36 months on a series of 540 cases of advanced carcinoma of the prostate without metastasis when first seen which were treated by the various types of endocrine therapy in common use to-day. To the above we have added our series of 25 cases which were treated by the combined therapy (table 1). One cannot examine these results without experiencing a feeling of profound gratitude for the progress that has been made in the treatment of carcinoma of the prostate during this last decade. Whereas the survival rate for 36 months was but 20 per cent in the control series, it was 66 per cent in the castration and stilbestrol group and 84 per cent in the patients who were treated by the combined endocrine and radical prostatectomy method. While we realize it would be unwise to attach too much significance to the results of a comparative study in which one group is much smaller than the others, it is interesting to note that the per cent of deaths not due to cancer in the small group was very close to that of the other groups.

We think that our results are sufficiently encouraging to warrant further trial of this therapy. Even if in our future cases the carcinoma is not as satisfactorily controlled, we believe that this treatment in most instances, where judiciously used, will prolong the life of the patient and increase his period of freedom from the distressing urinary symptoms that almost inevitably accompany the late stages of this disease. As pointed out previously, the operation entails little or no more risk than other open operations for relief of prostatic obstruction. Furthermore, the introduction by Vest of the traction suture method of anastomosing the vesical neck and the membranous urethra has done much to prevent the incontinence that occasionally resulted from this type of surgery.

CONCLUSIONS

The results obtained in the first 25 of a series of 31 selected cases of advanced carcinoma of the prostate that were treated by endocrine therapy combined with a follow-up, radical perineal prostatectomy and followed three years or more have been presented and discussed.

While this report has not been submitted as an evaluation of the ultimate mortality in such cases, we believe the results to date warrant a further trial of this therapy, not only by us, but by others.

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ENDOCRINE INHIBITION AS RELATED TO CARCINOMA OF THE PROSTATE

WILLIAM L. VALK AND ROBERT H. OWENS
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The prostate is an androgen target organ. Its normal growth and function are stimulated by testosterone. The growth of the neoplastic prostate may be stimulated by androgenic activity. For 11 years, extensive observations have been made concerning the benefits of orchiectomy and estrogen administration in the treatment of patients with carcinoma of the prostate. The anti-androgen approach obtains dramatic results in some 60 per cent of patients with disseminated carcinoma of the prostate. These patients, however, almost invariably have a relapse and are usually the eventual victims of cancer.

There has been widespread investigation as to the source of extragenital androgens which could be responsible for the reactivation of these carcinomas. The reticular zone of the adrenal cortex is a known androgen producer and its secretions, at least in certain pathological conditions, are capable of creating radical changes in the secondary sexual characteristics. In 1945, Huggins and Scott first performed bilateral adrenalectomy on patients with relapsing carcinomas of the prostate.[1] Inadequate adrenal replacement therapy made this procedure impractical until cortisone became available in 1951. Since then Huggins and Bergenstal have reported 14 cases of bilateral adrenalectomies on patients with relapsing carcinoma of the breast and prostate.[2] Many clinics throughout the country at this time are doing bilateral adrenalectomy for carcinoma of the breast and prostate.

Early observations with cortisone showed that excessive or prolonged use would suppress endogenous adrenal function.[3] Wilkins and his associates showed that as little as 25 mg. of cortisone acetate given orally each day would suppress excessive androgen production in patients with adrenal cortical hyperplasia.[4] In 1951 we began using cortisone to treat patients with relapsing carcinoma of the prostate. It was our hope to suppress adrenal androgen production and to gain a remission in patients previously shown to have been benefited by anti-androgen therapy. Cortisone was given in combination with stilbestrol in an effort to suppress the formation of gonadotrophins as well as suppressing adrenal function. We shall show later why we feel this is important.

Huggins has compared the pituitary-gonadal relationship to a closed-cycle

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Read at annual meeting, South Central Section of American Urological Association, Kansas City, Mo. September 21–23, 1953.

Cortone acetate generously supplied by Merck and Company.

Aided in part by Public Health Grant #H-1653 (C-3).

[1] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic cancer. Ann. Surg., **122:** 1031–1041, 1945.

[2] Huggins, C. and Bergenstal, D. M.: Inhibition of human mammary and prostatic cancers by adrenalectomy. Cancer Res., **12:** 134–141, 1952.

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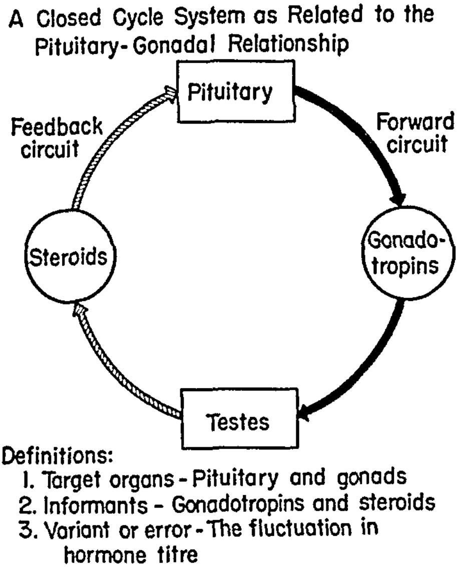
A Closed Cycle System as Related to the Pituitary-Gonadal Relationship
Pituitary
Feedback circuit
Forward circuit
Steroids
Gonado-tropins
Testes
Definitions:
1. Target organs - Pituitary and gonads
2. Informants - Gonadotropins and steroids
3. Variant or error - The fluctuation in hormone titre

FIG. 1

feed-back electrical circuit.[5] This is indeed an interesting speculation. It is realized, of course, that the human being does not respond in a linear fashion and the effects are not always proportional to the causes. Regardless of this, it is stimulating to inspect the endocrine system in relation to certain rules of feed-back.

In a closed-cycle feed-back system (fig. 1), the variant or error causes the target to measure, compare, and correct so that the actual value is changed to the desired value. If the input oscillates in value, then the output quantity will also oscillate in value. This causes successive quantities around the loop to oscillate. When the time lag of the response adds up to one-half the cycle, the feed-back maintains its assumed motion. By increasing the amount of the informant, oscillation is increased and by increasing the frequency of the informant, there is an increase in the time lag of the response. The mechanical methods to prevent these dilemmas are to quicken the target response, divide the target into many points of action, and to develop target anticipation or time lead. The nervous system is an example of time lead. The output impulses occur before the maximal stimulus, thus preventing overshooting or oscillation.

In the pituitary-gonadal system, we have a complex group of feed-backs which for the most part are unmeasurable and little understood. It is possible that order is maintained in this system by dividing the point of action over a number of functioning cells or by damping the informant by modifications occurring in the

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TABLE 1.—*Living Patients*

<table>
<tr><th rowspan="2">PATIENT</th><th rowspan="2">TUR AND ORCHIECTOMY</th><th rowspan="2">LENGTH OF STILBESTROL ℞ UNTIL RELAPSE</th><th colspan="4">LENGTH OF CORTISONE ℞ IN MG</th><th rowspan="2">COMPLICATIONS</th><th rowspan="2">RESULTS</th></tr>
<tr><th>Over 300</th><th>200</th><th>100</th><th>25–50</th></tr>
<tr><td rowspan="2">1. W. C.
Age 68
C. male</td><td rowspan="2">May '52</td><td rowspan="2">10 mo.</td><td>21 d.</td><td>2 d.</td><td>3 d.</td><td>5 mo.</td><td rowspan="2">Edema and cardiac failure</td><td rowspan="2">Pain free. Acid phosphatase dropped from 1.7 to .8 mm.</td></tr>
<tr><td colspan="4">Total 6 mo.</td></tr>
<tr><td rowspan="2">2. J. B.
Age 57
W. male</td><td rowspan="2">May '51
Nov. '51</td><td rowspan="2">3 mo.</td><td>15 d.</td><td>0</td><td>47 d.</td><td>17 mo.</td><td rowspan="2">Edema
Bleeding ulcer</td><td rowspan="2">Symptomatically well. Pain free. Acid phosphatase normal</td></tr>
<tr><td colspan="4">Total 19 mo.</td></tr>
<tr><td rowspan="2">3. V. T.
Age 66
C. male</td><td rowspan="2">Jan. '47</td><td rowspan="2">75 mo.</td><td>5 d.</td><td>7 d.</td><td>8 d.</td><td>12 mo.</td><td rowspan="2">None</td><td rowspan="2">Pain free. Acid phosphatase normal</td></tr>
<tr><td colspan="4">Total 13 mo.</td></tr>
<tr><td rowspan="2">4. O. E.
Age 64
W. male</td><td rowspan="2">May '51
May '52</td><td rowspan="2">7 mo.</td><td>17 d.</td><td>2 d.</td><td>3 d.</td><td>7½ mo.</td><td rowspan="2">None</td><td rowspan="2">Pain free. Acid phosphatase dropped from 6.0 mm. to 2.1 mm.</td></tr>
<tr><td colspan="4">Total 8½ mo.</td></tr>
<tr><td rowspan="2">5. A. T.
Age 76
W. male</td><td rowspan="2">Feb. '52</td><td rowspan="2">0</td><td>42 d.</td><td>3 d.</td><td>8 d.</td><td>17 mo.</td><td rowspan="2">Edema</td><td rowspan="2">Symptomatically well. Pain free. Acid phosphatase normal</td></tr>
<tr><td colspan="4">Total 19 mo.</td></tr>
</table>

Cortisone inhibits adrenal cortical function by inhibiting the adrenocorticotrophic hormone of the anterior pituitary. There is some evidence that cortisone may inhibit the production of the luteinizing hormone.[10] Sohval and Soffer have demonstrated that cortisone causes an increase in the urinary excretion of follicle stimulating hormone.[11] Since cortisone inhibits ACTH and possibly the luteinizing hormone, and stilbestrol inhibits the follicle stimulating hormone, it would appear that the combination of cortisone and stilbestrol would not only inhibit endogenous adrenal function but would also inhibit the production of gonadotrophins. Neither cortisone or stilbestrol by itself could satisfactorily perform this function. The gonadotrophins, we feel, are either directly or indirectly the prime source of stimulus to the endocrine responsive tumors and hence should be a prime target in therapy.

Twelve patients with relapsing carcinoma of the prostate were treated with a combination of cortisone and stilbestrol. All but one of the patients had previous orchiectomy and stilbestrol therapy. The length of time elapsed since the institution of orchiectomy and stilbestrol therapy varied from 3 to 75 months with an average of 20.2 months. This indicates that patients, all of whom had metastatic carcinoma of the prostate at the time of their original diagnosis, had gone for an average of 20.2 months until they had relapses. The age in this group varied from 57 to 75 with an average age of 65.5. There were 8 white patients and 4 Negros treated. Eight of these patients had elevated acid phosphatases and all of the patients had either osteoblastic or osteolytic metastases.

Tables 1 and 2 briefly summarize the course, length of treatment and results obtained from treatment. As will be noticed, treatment consisted of varying

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[10] Antopol, W., Glaubach, S. and Quittner, H.: Experimental observations with massive doses of cortisone. Rheumatism, 7: 187–196, 1951.

[11] Sohval, A. R. and Soffer, L. J.: The influence of cortisone and adrenocorticotrophin on urinary gonadotropin excretion. J. Clin. Endocrinol., 11: 677. 1951.

TABLE 2.—*Dead Patients*

PATIENT	TUR AND ORCHIECTOMY	LENGTH OF STILBESTROL ℞ UNTIL RELAPSE	LENGTH OF CORTISONE ℞ IN MG				COMPLICATIONS	RESULTS
			Over 300	200	100	25–50		
1. J. M. Age 65 W. male	June '49 Dec. '49	35 mo.	56 d.	7 d.	9 d.	0	Salt retention Edema Pneumonia	Expired on 1-20-53 of influenza and bronchopneumonia
			Total 2½ mo.					
2. W. M. Age 75 W. male	Nov. '51 Dec. '51	11 mo.	55 d.	2 d.	11 d.	0	Salt retention Edema Nasal infection Influenza	Expired on 1-25-53 of carcinomatosis and influenza
			Total 2½ mo.					
3. A. G. Age 65 C. male	Jan. '52	8 mo.	30 d.	16 d.	12 d.	1 mo.	Tuberculosis activation	Expired suddenly of coronary thrombosis
			Total 3 mo.					
4. E. T. Age 66 W. male	March '51	9 mo.	34 d.	4 d.	21 d.	4 mo.	Edema Salt retention Cardiac failure	Expired after cortisone stopped by patient
			Total 6 mo.					
5. R. N. Age 67 W. male	June '50 July '50	15 mo.	12 d.	2 d.	11 d.	8 mo.	Salt retention Edema Cardiac failure	Expired of pneumonia after cortisone stopped by patient
			Total 9 mo.					
6. S. C. Age 70 W. male	June '49	33 mo.	17 d.	0	0	5 mo.	Marked edema Cardiac failure	At no time showed clinical improvement
			Total 6 mo.					
7. R. S. Age 60 W. male	Jan. '51 Feb. '52	6 mo.	61 d.	5 d.	10 d.	10½ mo.	Salt retention Edema	Expired July '53
			Total 13 mo.					

dosage of cortisone given with stilbestrol. Any dose of cortisone over 100 mg. a day was considered to be in the therapeutic range and doses over 300 mg. per day in the toxic range. As has been previously stated, it was our desire not only to cause adrenal inhibition, but also to inhibit the anterior pituitary. An initial dose of cortisone of 300 mg. or over was given for as long as 61 days and doses of 100 mg. or over were continued for as long as 76 days. The patients were then placed on maintenance doses of 25–50 mg. of cortisone and 5 mg. of stilbestrol. These medications were to be continued for the rest of their lives.

The subjective results showed marked relief of pain and, generally speaking, increased vigor and activity. Pain relief continued beyond the large doses of cortisone and was just as marked on maintenance levels. Several patients experienced pain when stilbestrol was stopped even though they were still on cortisone therapy.

Objectively, these patients showed little change in the size or shape of their prostates. Their hemoglobin remained the same and other than from edema, there was little actual weight gain. Bony metastases as shown by x-ray showed regression in only one case. The acid phosphatase levels fell in 8 out of 12 cases. The response of the acid phosphatase to treatment appears to depend on a combination of cortisone and stilbestrol therapy, as will be discussed in more detail later.

Five patients in this series are still living and relatively well. Three of these patients are what might be classified as clinical remissions. Two of these patients have gone 19 months since the institution of therapy.

Seven patients have expired since treatment was begun, either from their original carcinomas or some complicating factors. The complications on large doses of cortisone are frequent and severe. Two patients in this series expired after they had inadvertently stopped cortisone for a period of one to two weeks. One of the two was admitted to the hospital in extremis and expired with all of the clinical signs of adrenal insufficiency. Three patients developed influenza while on therapy. Their clinical course was severe, in spite of antibiotics and supportive therapy; two of these patients expired. Two patients died of progressive carcinoma and one patient died of a coronary thrombosis after he was in an apparent clinical remission.

An effort to follow the activity of the carcinoma was made by frequent acid phosphatase readings. At first it was distressing to note that on large doses of cortisone alone the acid phosphatase actually went up. Later it was found that when stilbestrol was added and the cortisone dropped to maintenance levels, the acid phosphatase dropped to normal or far below precortisone levels. Since these patients had previously been on stilbestrol and the acid phosphatase levels were better than those of pretreatment level, it became apparent that cortisone and stilbestrol must have some synergistic reaction in inhibiting tumor activity. Figure 3 shows the precortisone and maintenance cortisone levels of acid phosphatase.

Figures 4 and 5 graphically show the course of the alkaline and acid phosphatase of two typical patients while on therapy. They illustrate that the acid phosphatase did not return to normal until maintenance levels of cortisone were reached.

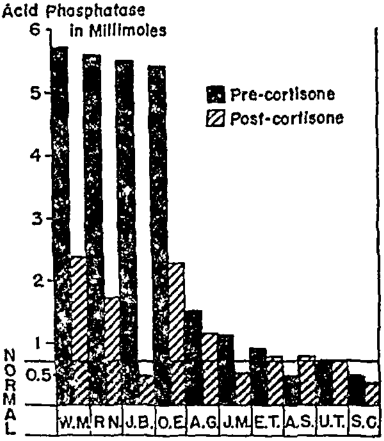

FIG. 3

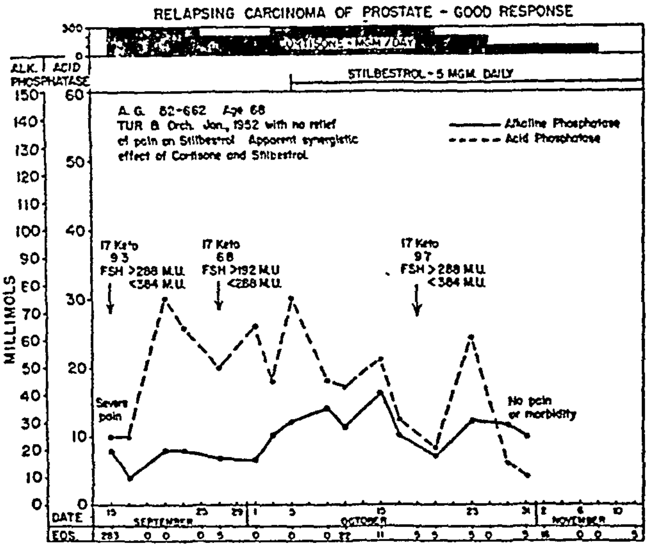

FIG. 4

Seventeen-ketosteroid studies were made at regular intervals in all patients. Table 3 shows the steroid pattern in 9 pre- and post-cortisone-estrogen treated patients. Cortisone is broken down in part and excreted as 17-ketosteroids in the urine. This will increase the urinary excretion of 17-ketosteroids. While on large dosage of cortisone, the steroid levels were usually fairly high. After maintenance levels were reached, however, in most instances the steroids fell. In the one patient who stopped taking cortisone, there was only .9 mg. of ketosteroids excreted in 24 hours, indicating almost total adrenal inhibition.

Assay of the gonadotrophins was attempted, but considered unreliable. Ideally a more specific manner of measurement of the gonadotrophins is necessary before these changes can be properly evaluated.

In this series cortisone was used in excessive dosage. For this reason, we

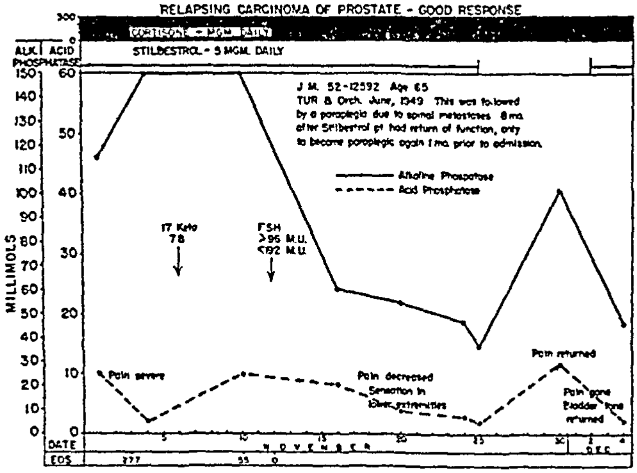

FIG. 5

TABLE 3 *17 Ketosteroid excretion before cortisone estrogen treatment and while on maintenance dosage*

PATIENT	PRE TREATMENT LEVEL IN MG	MAINTENANCE LEVEL IN MG
W M	4 3	2 1
E T	8 6	9
J M	7 8	15 0
R S	4 4	4 8
V T	8 0	1 7
J B	20 8	3 52
W C	13 1	4 7
A T	20 85	4 6
O E	9 9	6 2

observed many toxic responses In large doses, cortisone causes salt retention, edema, and potassium loss All patients were given 3 gm potassium chloride per day and all had salt-restricted diets In spite of this, edema occurred in 8 of our 12 patients Mercurial diuretics were used periodically to combat edema but it was found that the edema was unusually persistent and did not readily respond to diuretics It was necessary to digitalize 4 patients in whom cardiac failure developed co existent with their edema

Diminished resistance to stress was probably the most severe complication that occurred As has been previously stated, two of our patients died of influenza Intermittent antibiotics were given most of the patients as a prophylaxis against intercurrent infection Two patients died after stopping cortisone, presumably of adrenal insufficiency Certainly any patient taking cortisone should be warned of this grave consequence and if it is necessary to stop cortisone for any reason, several days of ACTH therapy should be given The patients' adrenal function should then be checked with periodic Thorn tests to determine adrenal status

Cortisone causes an increased secretion of hydrochloric acid, and gastritis developed in a number of patients One patient had a bleeding peptic ulcer while on therapy Routine antacids are now given in an effort to prevent this complication

One patient with an old fibrotic lesion in the apex of the right lung had soften-

TABLE 4

1 Bilateral orchiectomy
2 Estrogen stilbestrol 5 mg /day for life
3 Cortisone—300 mg /day for 2 weeks
    200 mg /day for 2 weeks
    100 mg /day for 2 weeks
    25 mg /day for life
  a Low salt diet
  b KCl 2-3 gm daily
  c Antacid regimen if ulcer history
  d Diuretics as needed

ing and what the roentgenologist interpreted as activation of an old tuberculous lesion.

All patients showed slight early euphoria, but in no incidence were there any overt psychoses. Skin petechiae occurred in 4 patients. Osteoporosis was not marked while on a high protein intake. Most of these patients had an unusually good appetite and maintained a good nutritional status. No temporary or permanent hypertension or diabetes developed in any patient.

SUMMARY

Twelve patients with far-advanced relapsing carcinoma of the prostate were treated with a combination of cortisone and stilbestrol. The initial cortisone dosage given was high in an attempt to inhibit functionally the adrenal and the anterior pituitary. Stilbestrol was given as a necessary adjunct to pituitary inhibition.

Five patients are living and three of these are totally asymptomatic. Seven patients are dead; death occurred from progressive carcinomatosis or complications of therapy. The toxic responses to large doses of cortisone are frequent and severe. Urinary excretion of 17-ketosteroids was markedly depressed in 7 of 12 patients treated with cortisone and stilbestrol, indicating adrenal cortical inhibition.

Table 4 summarizes our regimen of treatment and necessary prophylactic measures.

It would appear from our small series of cases that about 40 per cent of the patients with far-advanced carcinoma of the prostate can obtain additional benefits from combination cortisone and stilbestrol therapy. These benefits are a great help in treating patients who have become refractory after previous orchiectomy and stilbestrol therapy.

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LATE RESULTS OF BILATERAL ADRENALECTOMY FOR ADVANCED CARCINOMA OF THE PROSTATE GLAND

WILLIAM J. BAKER

One year ago, a report was given to this Association on bilateral adrenalectomy for 10 patients whose carcinoma of the prostate gland and symptoms had not been adequately controlled by open prostatic surgery or revision of the obstructive vesical neck, estrogens, bilateral orchiectomy, with and without deep roentgen therapy, and oral cortisone. All of these patients were bedridden and required some form of opiate for their pain and discomfort. All patients had had a tissue diagnosis of cancer of the prostate gland. All patients had bone metastases. There was no immediate operative mortality. There was no difficulty in the postoperative management of these Addisonian individuals.

We have been impressed with the comfortable states of the majority of these patients after bilateral adrenalectomy. Only one patient failed to get relief from the procedure. All, except two, became ambulatory and euphoric. To be sure, there has been a recurrence of pain in all except one patient. He is alive and well almost 10 months. The recurrent pain has usually been less severe than the original pain. The patients who require small amounts of analgesic for their recurrent pain, have led a much more comfortable existence than they did before bilateral adrenalectomy. In 2 patients, whose pain returned, a short course of deep x-ray therapy over the painful regions, gave almost complete relief. X-ray therapy over these same regions, before bilateral adrenalectomy, had given no relief.

The youngest patient in this group was 47 years, the oldest was 76 years. The patients who have lived the longest after bilateral adrenalectomy were 57, 58, 60 and 61 years old. The age of the patient could not be related to the amount of relief which was obtained from metastatic pain. The patient who obtained no relief from the procedure was 59 years old.

Adrenalectomy for cancer is predicated on the fact that the adrenal gland is involved in the growth of neoplastic tissue. It is known that people with cancer have abnormal amounts of normal adrenal steroids. It is also known that people with cancer have steroids that are not found in other people. However, after bilateral adrenalectomy in patients with advanced cancer of the prostate gland, serial x-rays of osseous lesions, serial acid and alkaline phosphatase determinations, serial rectal examinations, serial body weight and hemoglobin determinations and serial androgen values have furnished us no evidence that the prostatic cancer or its metastases have been inhibited. As far as we can ascertain, the cancer continues to grow at its usual rate. Figure 1, *A* is the picture of obvious metastastic bone lesions of one of these patients before bilateral adrenalectomy. Figure 1, *B* is a picture of the same lesions 7 months after bilateral adrenalectomy. Figure 2, *A* is the x-ray picture of obvious metastatic bone lesions of another patient before bilateral adrenalectomy. Figure 2, *B* is a repeat picture of this same patient 9½ months after bilateral adrenalectomy. Figure 3 is the final

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Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

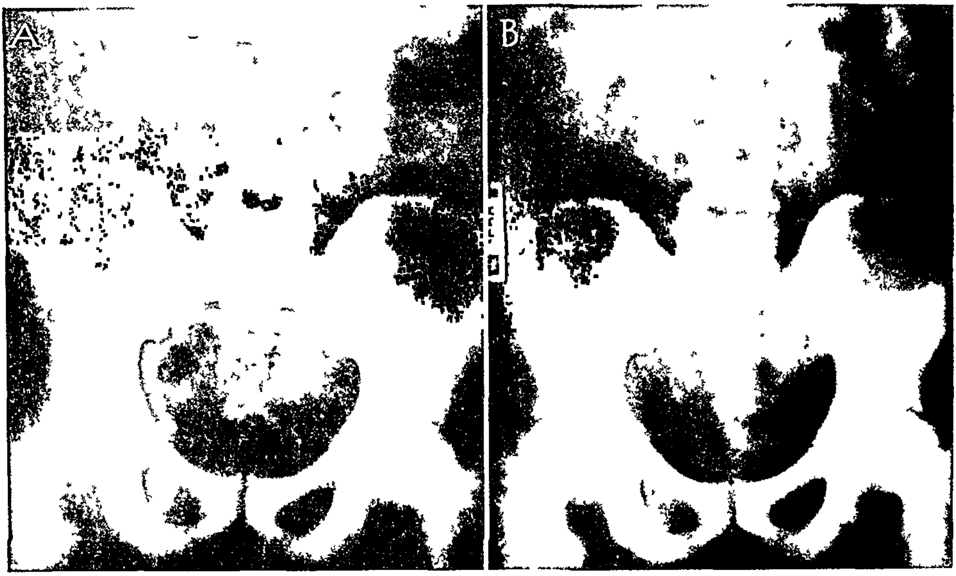

FIG. 1

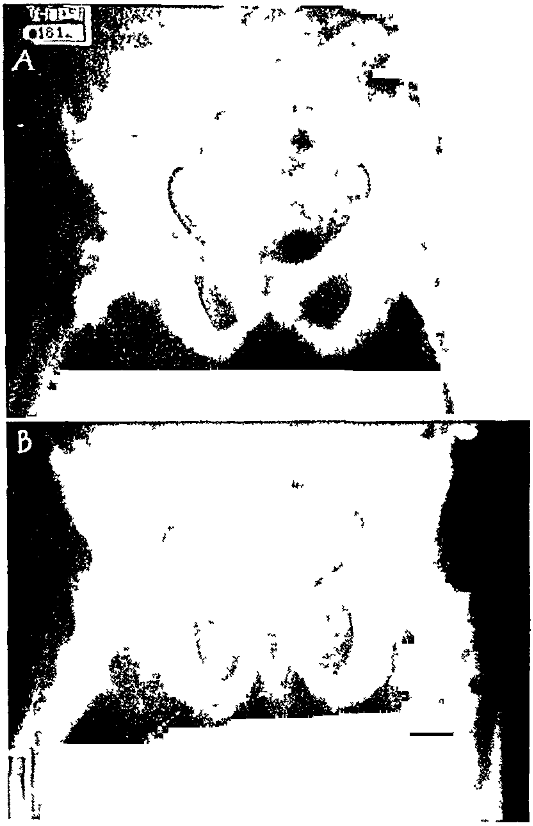

FIG. 2

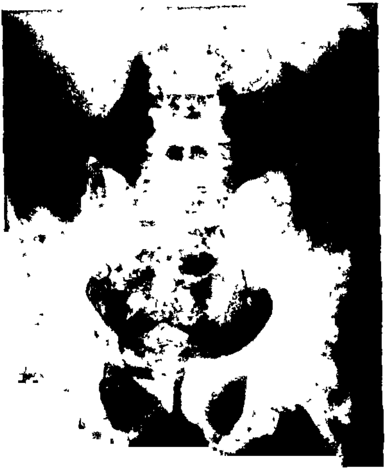

FIG. 3

picture of this patient's bones just before he died, or 13 months after bilateral adrenalectomy. The metastatic bone lesions of these two patients were obviously not retarded. It is certain that no bone metastases disappeared in these pictures. It must be admitted that, occasionally, bony metastases seem to grow more sclerotic after adrenalectomy. We have never seen them become smaller or disappear.

What about the life expectancy of the man with advanced prostatic cancer, who has had bilateral adrenalectomy? Tables 1 and 2 show that only two out of eleven of our patients are alive. The longest time that any of our patients lived after this procedure is 1 year, 1 month, 11 days. One patient is alive 1 year, 22 days after the procedure. This man has recently complained of severe pain which requires Demerol for control. Another patient is alive 9 months, 20 days. He had minimal persistent discomfort after bilateral adrenalectomy. A course of deep roentgen therapy caused complete disappearance of the discomfort. He takes no sedatives or analgesics, is ambulatory, euphoric and working. The other 9 patients lived from 1½ months to 1 year, 11 days. Thus, it can be seen that there has been no striking prolongation of life in this group.

All of our patients have died relatively suddenly. They were ambulatory one day and in a terminal state the next day. Most of them have become weak, apathetic and finally comatose, all within a very few hours. Blood chemistry studies have not revealed striking changes even on the day of death.

Four complete autopsies have been performed on patients who have had bilateral adrenalectomy for advanced prostatic cancer. No residual adrenal tissue was found in these four bodies. No tissue had been spared from invasion by the cancer cells.

TABLE 1. *Late results of bilateral adrenalectomy for advanced carcinoma of the prostate gland*

RACE	AGE	SURVIVAL TIME	NARCOTICS REQUIRED	TYPE OF DEATH	AUTOPSY—REMARKS
T. P., Negro, St. Luke's Hospital	48	6 months 1 day	Needed codein last month of life	Collapsed suddenly and died in 2 hours	Generalized carcinomatosis. No other adrenal tissue found
I. S., White, Cook County Hospital	59	5 months 3 days	Demerol the last 4 months of life	Generalized edema and coma last 2 days of life	Generalized carcinomatosis. Metastases in pituitary gland. No other adrenal tissue found
C. G., Negro, Cook County Hospital	61	1 year 1 month 11 days	Required codein and Demerol last 3 months of life	Developed very severe anemia. Many transfusions. Always euphoric. Sudden death	No autopsy
B. T. W., Negro, Cook County Hospital	47	3 months 5 days	Demerol last 2 months of life	Died suddenly. In coma for 2 hours	Generalized metastases. Large metastatic growth around old gunshot wound of hip. No adrenal tissue found
J. M., Negro, Cook County Hospital	57	1 year 1 day	Demerol last 6 weeks of life	Always had troublesome gas "on stomach". Died during sleep	Generalized metastases. Each ureter was partially obstructed by a metastatic tumor. Original blood pressure 220/110. Adrenalectomy did not alter hypertension. No adrenal tissue found

TABLE 2. *Late results of bilateral adrenalectomy for advanced carcinoma of the prostate gland*

RACE	AGE	SURVIVAL TIME	NARCOTICS REQUIRED	TYPE OF DEATH	AUTOPSY—REMARKS
A. N., White, St. Luke's Hospital	65	6 months 9 days	Demerol required last 4 months of life	Died very suddenly. Ambulatory until day of death	No autopsy
S. G., White, St. Luke's Hospital	76	5 months 9 days	Codein required last 2 weeks of life	Sudden collapse and death while campaigning for Taft	No autopsy
E. N., White, Cook County Hospital	60	Still alive and well. 1 year 22 days	Has fleeting pains. Takes no sedatives		
C. B., White, St. Luke's Hospital	62	1 month 15 days	No sedatives required	Lethargic and catatonic for 6 weeks. Slow death	No autopsy
J. Z., White, St. Luke's Hospital	54	3 months 10 days	No relief from metastatic pain	Sudden death. One hour of coma	No autopsy
T. T., Japanese, Cook County Hospital	58	Still alive and well. 9 months 20 days	No sedatives required		Complete relief from pain after x-ray therapy following adrenalectomy

It can be seen that the evaluation of this procedure is made entirely on the subjective response of the patient. The relief of pain is usually striking. The patients who have been bedfast because of pain, feel better almost immediately and want to get out of bed in a few days. Their appetite becomes ravenous and the replacement therapy with cortisone usually produces an euphoric state. The occasional patient will be rehabilitated enough to resume his former work. Most of our patients have never returned to their work.

The past year has brought to our attention that the patient who fits our indication for this procedure has become very scarce.

Cook County Hospital is a haven for end pathology. It has furnished us only one patient for our series. Four excellent residents have endeavored to find such patients. St. Luke's Hospital has not furnished a single private patient for our series. One wonders whether prostatic cancer is changing its biological behavior.

It is believed that bilateral adrenalectomy is an excellent procedure for the relief of metastatic pain from advanced prostatic cancer of patients whose pain is not adequately controlled by castration, estrogens, deep roentgen therapy or oral cortisone.

In conclusion, the thought should be left with you that there is evidence that some cancers of the prostate gland seem to be independent of androgens and the search for related stimulating or inhibiting factors should be continued diligently.

7 W. Madison St., Chicago 2, Ill.

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APPRAISAL OF PRESENT METHODS OF TREATMENT OF ADVANCED PROSTATIC CANCER

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Until receipt of the program for this meeting and particularly until I had read the titles of the papers constituting this symposium, I had little idea as to what I should present under the title which Dr. Heckel assigned to me.

Dr. Scott has just presented to you an evaluation of hormonal therapy followed by radical perineal prostatectomy in selected cases of advanced carcinoma of the prostate. You will recall that Dr. Colston and Dr. Brendler, of our Institute, presented a preliminary report on this subject in an issue of the J.A.M.A. for 1946. Whereas I believe that Dr. Scott has handled the subject in a splendid fashion and has demonstrated the merits of this regimen in certain selected cases, I am of the opinion that in this instance, as well as in all instances of studies involving the treatment of cancer of the prostate, insufficient attention has been paid to the "biological potential" of the cancer. Admittedly, we have used almost all of the yardsticks available to us at present, but none really tell us the degree of malignancy of any given cancer, and hence are of little prognostic value.

May I attempt to illustrate what I am driving at by referring to two patients recently seen again at the Brady Institute: The first, a man aged 75, was seen in 1928 with signs and symptoms of a benign obstructing prostate. A simple perineal enucleation was carried out at that time, and sections made on the tissue removed revealed adenocarcinoma. Within one year, although there were no signs of metastasis, examiners felt that the cancer had extended beyond the capsule of the gland and that total prostatectomy was not indicated. The patient was lost track of until approximately 6 weeks ago when he returned to the dispensary in acute retention. On rectal palpation the prostate was large and nodular. It was judged cancerous and definitely inoperable. Serum acid phosphatase levels were normal and x-rays revealed no evidence of metastasis. A transurethral resection for relief of obstruction was done and sections on this tissue showed adenocarcinoma indistinguishable from that removed 25 years previously. In any series, this would be a 25 year cure, no matter what was done.

A second case is similar. The patient, seen by Dr. Colston in 1941, was believed to have an early operable prostatic cancer. A perineal biopsy revealed a small nodule which on frozen section proved to be adenocarcinoma. A total prostatectomy was done at the same sitting and yet multiple permanent sections failed to reveal any cancer, indicating that the biopsy was generous and had removed the entire cancerous nodule. The patient did exceptionally well until 1951. As a matter of fact, he continues to do well, and yet since 1951 his bones are seen to be riddled with cancer and his serum acid phosphatase is elevated. Endocrine treatment is now being given.

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6-8, 1953.

Based on these two cases alone, one might be inclined to think that adenocarcinomas were less malignant than undifferentiated prostatic cancers, and yet a previous attempt at correlating the length of survival with cell types has led me to believe that no significant relation exists and that one cannot predict on the basis of cell type the response to any particular form of therapy

I will be very much interested to hear the follow-up reports to be presented by Dr Baker and by Dr Harrison on the subject of bilateral adrenalectomy for advanced prostatic cancer You will recall their preliminary reports of last year Since last year we have done no more bilateral adrenalectomies As a matter of fact, we have only performed two for prostatic cancer, one surviving a few months and one dying within the last two months, some 15 months after both adrenals were removed Recently, these two cases were presented at the clinical pathological conference held weekly in our Department of Pathology by Dr Arnold Rich One thing in particular interested me Whereas there was definite evidence in certain areas of the prostate that certain cancer cells had undergone atrophy, immediately adjacent to these areas were areas of perfectly good cancer which seemed to be uninfluenced by anything that had been done to the patient Furthermore, sections of untreated prostatic cancer in patients before the days of endocrine management were presented and often showed identical changes I do not mean for a minute to leave you with the impression that I think that prostatic cancer has not been influenced by endocrine manipulations or that further advances will not be made If I thought this, I would discontinue many studies currently in progress involving endocrine relations in prostatic growth I do mean to emphasize, however, that the nature of our controls leaves much to be desired

Recently, in completing a monograph on *The Surgery of the Adrenal Glands* as one of the American Lecture Series in Surgery, I reviewed all the cases of adrenalectomy done to date, not only for prostatic cancer but for cancer of the breast as well Time does not permit review of these data, however, I will read to you the most recent results in a series of 10 patients adrenalectomized for prostatic cancer and reported by the Memorial Hospital group "Three died in the immediate postoperative period, one from cerebral hemorrhage (2 days), one from carcinomatosis (11 days) and one from myocardial infarction (21 days) Six of the remaining seven died within 33 to 294 days after adrenalectomy, two from adrenal insufficiency and four from cancer " The remaining patient was living at the writing of this addendum, his 159th postoperative day Quoting further· "All seven patients had temporary subjective improvement varying from 14 to 210 days, averaging 82 days Only two of the seven had objective improvement lasting 90 and 133 days The most striking beneficial response to adrenalectomy was relief of pain " There has not been a publication from the Huggins laboratory on adrenalectomy for prostatic cancer since that of Huggins and Bergenstal, to be found in *Cancer Research* for 1952, and the results in this series of 7 patients are quite comparable to those of the Memorial Hospital group Of the seven there was one postoperative death, and they judge that three of the remaining six had a clinical remission of the disease of considerable magnitude One patient died of acute pulmonary edema 49 days after adrenalectomy. The remaining four had been observed for periods of 4½ to 9 months at the time of the report. Quoting them: "Perhaps the most striking observation has been the immediate and persistent relief of crippling pain in the bones." In conversation with Dr. Huggins since this report, I have learned that he is performing fewer and fewer bilateral adrenalectomies for prostatic cancer and more and more for cancer of the female breast.

Unfortunately, in most studies to date an insufficient amount of time and effort has been spent in determining the mechanism of action of bilateral adrenalectomy, and it is my feeling that until such is done, little further advance will be made. During the past year there has been further evidence to support the statement which I made at this same meeting in 1952 that cortisone, so necessary in the maintenance of the bilateral adrenalectomized human, is metabolized to androgen. Again this is hard to reconcile with theories which assign improvements following adrenalectomy to androgen withdrawal. Cortisone alone has been as effective at times as adrenalectomy. At present it is my opinion that adrenalectomy for cancer of the prostate and breast is empirical, as Huggins suggests the administration of androgen or estrogen is for advanced breast cancer in the female. If results were better than they are to date, one would be justified in advising this procedure in the individuals hopelessly afflicted with these cancers. In that they are not, it is my belief that these should be considered as research tools and only carried out in institutions equipped for research.

The same holds true for hypophysectomy. One year ago I reported to you on the results in 3 cases of disseminated prostatic cancer subjected to hypophysectomy. Since then, two more cases have been studied. One of these died within a few days after operation, and the other is alive and clinically in fair condition some 6 months after operation. To date total hypophysectomy has not been possible, probably because of the difficulties of exposure, and we are considering ablation of that portion of the pituitary which cannot be removed by radioactive means. In attempting to evaluate the procedure to date, I can simply say that in the two individuals with close to total hypophysectomy, one living 5 months and coming to autopsy and one alive at present, the effects have been comparable to those observed following adrenalectomy. In one whose testes were intact at the time of hypophysectomy, the effects were strikingly like those following castration. We do not recommend the procedure to any of you, but will continue to use it in selected cases in an effort to learn more about this disease.

What the future holds, no one knows, but I am firm in my belief that we will make more progress by carefully studying endocrine effects on prostatic growth in the animal, with careful clinical studies when indicated, than to attempt to draw conclusions from a statistical study of a huge series of patients subjected to any one of a number of endocrine procedures. As I have attempted to point out in an article in the 1952 *Transactions of the Western Section of the American Urological Association* entitled, "What Makes the Prostate Grow," much more must be learned concerning the effects of estrogen withdrawal, estrogen being a secretion of the testis as well as androgen. Much more must be learned of the precise nature of the chemical substances liberated by the testes and by the adrenals. If we were to know more, we could predict with a fair degree of accuracy what analogs or, in other words, closely related steroids, would act as inhibitors of circulating biological gonadal and adrenal steroids. If we were to know more about the effects of the pituitary on benign and malignant prostatic growth, we could design better experiments directed towards chemical inhibition of pituitary action.

The road ahead is long and hard. Someone might make a discovery tomorrow which might put us ahead many years, but I doubt it. I do not think this is a pessimistic attitude but a realistic one. A pessimist would not be in this field. Being a realist, I think that for the immediate future we, as urologists, should make every effort to educate the public and the physician in the early recognition of prostatic cancer, at a time when it is operable and at a time when total prostatectomy in the hands of most offers a 50 per cent chance of 5 year survival without cancer. In the meantime, many of us in our laboratory will endeavor to unravel some of the problems discussed. These largely revolve around the early chemical detection of prostatic cancer, the biological potential of any given tumor, the metabolic action of steroids and the nature and action of competitive steroids.

We have made no progress in the chemical detection of early prostatic cancer, although we are continuing a program of fractionation and identification of urinary steroids hoping to find some one specific for prostatic cancer.

For some time we have considered and have now initiated a program in which we are attempting to correlate survival of human prostatic cancer in the anterior chamber of the guinea pig eye with the degree of malignancy as determined by the clinical course of the disease—a search for the "biological potential."

To date we have been unable to demonstrate any *in vitro* effects of androgens or estrogens on human and animal prostatic slices. We have observed, however, a profound differential *in vivo* inactivation of androgens by the altered liver. This is contrary to our findings using estrogens.

Lastly, a lengthy program is in progress aimed at finding analogs of androgens. In a few years we may have something to report.

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A TRUE HERMAPHRODITE

ARTHUR B. CECIL

Since the founding of this Association in 1886, only 2 cases of true hermaphroditism have been reported before it. These two cases were reported in a paper by Kiefer and McKenna in 1944. The condition of rarity alone, however, would not prompt me to present this subject to you. I have decided to do so because I wish to discuss some original ideas in regard to the surgical treatment of intersexuality.

A. D. 0-7161, aged 6, who had been raised as a boy, was admitted to the Hospital of the Good Samaritan in Los Angeles, California, on December 2, 1935. The case was considered one of male pseudohermaphroditism. The penis showed ventral curvature, below which was a groove running into a urogenital sinus. There was no scrotum, nor could testicles be palpated. At this admission to the hospital a first-stage hypospadias operation was done for straightening of the penis.

The patient was lost sight of for 13 years, and was again admitted to the hospital of the Good Samaritan on August 17, 1948, at which time he was 19 years old (H.G.S. No. B.B. 8080). He had graduated from high school and had lived as a boy. The family history showed that he had four brothers: 24, 22, 17 and 15, and one sister, 21, all living and well and normally formed as were his father and mother.

When patient was 13 years old, and again 5 months previous to this admission, he had had vaginal bleeding. The first time the bleeding lasted for 1 week, and the second time for 3 days. He had male inclinations and desires, but had never had intercourse. He was most insistent that he be constructed as a male. Physical examination showed an individual weighing 140 pounds, 5 feet 6 inches tall. The general contour was that of a female: the breasts fairly large, the nipples highly developed with pigmentation about them. The pubic hair was of female distribution. There was no beard (fig. 1, *A*).

The phallus was 4.5 cm. in length and 2.5 cm. in diameter. The ventral curvature had been cured by the previous operation. There was a dimple representing a glandular meatus. On the ventral surface was a moist area running down to the urogenital sinus. On each side of this groove were labia minora 4 cm. in length (fig. 1, *B*). Just outside of the external ring one could palpate a mass which was about 2.5 cm. in its largest diameter. This was thought to be an undescended testicle. Nothing was made out in the left groin, and no hernia was present on either side. On rectal examination one could palpate a small body which was probably a uterus. A vaginogram showed a capacious vagina and a filling of the uterus and tubes (fig. 2).

On August 28, 1948, I excised the labia minora and did a Thiersch operation for the development of a urethra from the glans penis to the urogenital sinus, leaving the patient to urinate through the urogenital sinus. This operation was entirely successful (fig. 3).

Read at annual meeting, American Association of Genito-Urinary Surgeons, Hot Springs, Va. May 6–8, 1953.

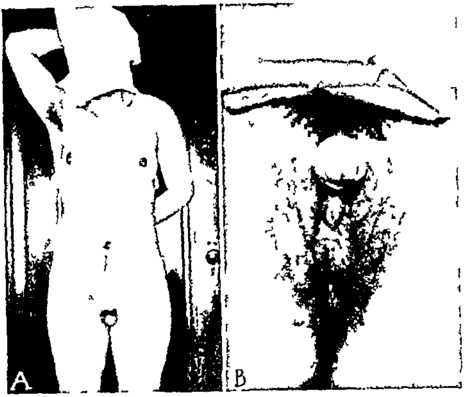

FIG 1

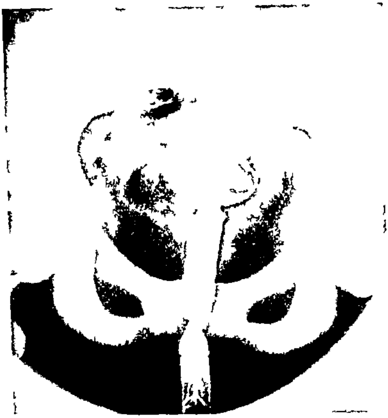

FIG 2

On November 29, 1948, abdominal and right groin exploratory operations were carried out by Dr Kenneth Blake and Dr Arthur Cecil

Total hysterectomy with bilateral oophorectomy and left salpingectomy, exploration of mass in the right groin Upon opening the abdomen the uterus was smaller than one would find in a female 19 years of age On the left side was a cystic ovary which measured 4 cm in diameter Lying above this was the left fallopian tube with its fimbriated end This cystic mass and left tube were removed The right tube was found to extend out into the right inguinal canal, and upon teasing it out with forceps, the fimbriated end was made out, but the tube could not be pulled into the abdominal cavity The uterus was removed just below the cervix After peritonealization, the abdomen was closed An incision

FIG. 3

was now made over the mass in the right groin. The tunica vaginalis was opened, and within it was found a most remarkable organ. A rounded mass 2.5 by 2 cm. was located. The lower pole, which made up half of the mass, was of a grayish color, and the upper pole showed ovarian follicles. There was a definite line of demarcation between these two bodies. Biopsy specimens were taken from both poles and immediately studied by Dr. John Tragerman. The lower pole proved to be a testicle, and the upper pole an ovary. The biopsy opening of the testicle was closed and the ovarian tissue dissected loose from the testicle and removed. The tube was left in because of fear of interfering with the blood supply to the testicle. No attempt was made to change the position of the testicle.

Pathological report (Dr. John Tragerman): "Uterus and cervix are removed together in a slender mass 8.5 by 3.8 by 2 cm. (fig. 4). The fundus is thin and soft showing considerable serosal congestion. The top of the fundus is slightly concave. The cervix is elongated measuring 3 by 2.1 by 1.8 cm. The lower uterine segment is also rather slender. The uterus and cervix are widely opened. The

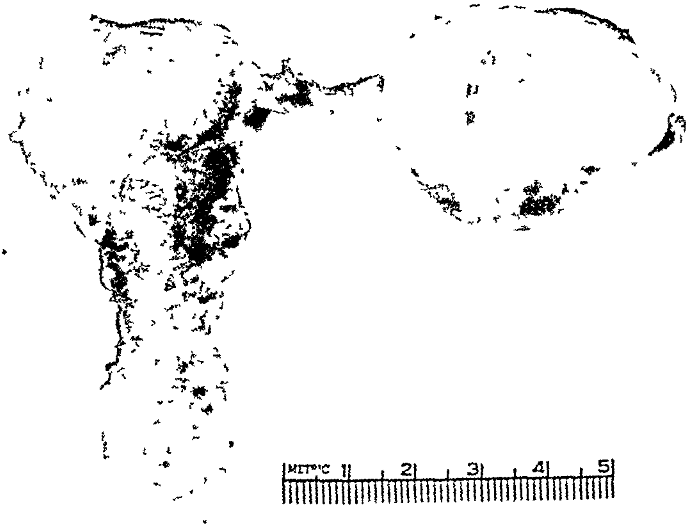

FIG 4

walls vary in thickness. The cervix shows a rather wide canal containing a few transverse corrugations and several mucous cysts. A cord-like band of pale tissue extends from one wall of the internal os upward for about 1.5 cm., and then seems to become incorporated with the endometrium above. The endometrium is less than 1 mm. thick, showing a number of small areas of hemorrhage. The cord-like tissue is nearly 3 mm. in diameter. A block is taken from the uterine wall, at each end of the cord and also from one cornu, where a firm 5 mm. nodule is somewhat suggestive of adenomyoma.

"Microscopic: The uterus shows a rather compact muscle and is lined by a thin irregular endometrium somewhat atrophic in appearance. The nodule in the cornu is suggestive of a small myoma but no glandular structures are present. A block from the internal os shows numerous mucous glands, a few of which are distended. There is also a deeper zone in the tissue containing glands and cysts more like those of the endometrium. The termination of the cord-like structure described grossly shows a projecting nodule of uterine muscle surrounded by a thin inactive layer of endometrium, as already noted. Anatomical diagnosis:—atrophic endometrium. Nabothian cysts of endocervix.

"Left tube and ovary are removed together, the tube measuring 5.5 by .6 mm. The serosa is smooth but quite congested. The tube is slender and tortuous. The distal end is patent. The ovary is a collapsed oval cyst 4.3 by 3.2 by 1 cm. (fig. 4). It has been widely incised through the lower border showing a smooth lined cavity presenting a gray red membrane streaked with congested vessels. A few small yellowish plaques appear in the lining and in the cyst wall. Several flattened follicular cysts of varying size are present in the cyst wall. A block is taken from the wall near the pole.

"Microscopic: The stroma is fairly dense, containing numerous primitive ova, a small follicular cyst and an organizing corpus albicans and a regressing corpus luteum. One field, however, indicates that there are some follicular cysts lining the large cavity. Anatomical diagnosis:—follicular cysts of left ovary.

"Sections A and B are from the right inguinal mass suspected as ovotestis. Section A, from upper pole of right inguinal mass, shows dense ovarian stroma containing numerous primitive ova and part of the lining of a partly collapsed follicular cyst (fig. 5, *A*). Section B shows a group of tubular structures supported by a rather hemorrhagic stroma. Along one surface is a narrow zone of fairly dense fibrous tissue. The cells in the tubules show considerable variation—some are large with granular eosinophilic cytoplasm, others show clear cytoplasm and eccentric nuclei with some tendency to rest near the basement membrane. Other tubules, however, are diffusely filled with similar cells and there is little suggestion of an acinal lumen. The appearance is that of an undeveloped testicle (fig. 5, *B*)."

December 29, 1948, third-stage hypospadias operation, Cecil: Suprapubic drainage was done, and an elliptical incision was made around the opening of the distal urethra and the urogenital sinus. This opening was closed in layers. On the eighth day the suprapubic drainage tube was removed, and at the next urination patient urinated through the urethra in the normal fashion (fig. 6).

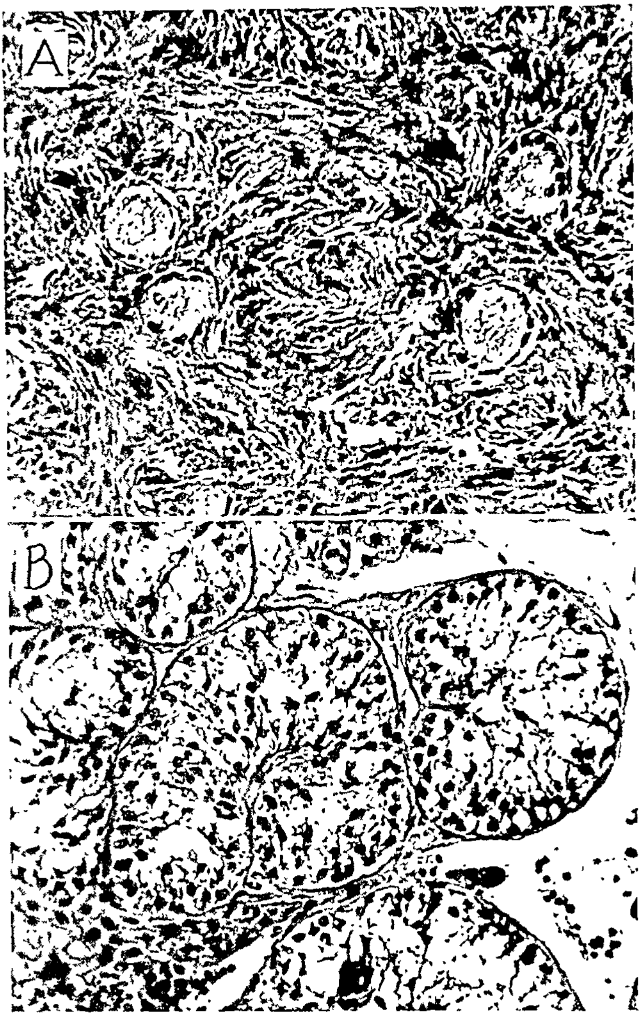

Fig. 5

The final stage in the male construction of this patient was the amputation of the breasts which was done by Dr. Kenneth Blake.

In 1942, Severinghaus[1] reported a study of the chromosomes of an intersex. In this case the secondary sex characteristics were a combination of male and female types. Exploration proved that the patient was a male pseudohermaphrodite. Biopsy specimens of the testicles were studied. The chromosomal content of the cells was found to be normal and the sex chromosomes corresponded with the gonadal sex. No studies of the chromosomal content of a true hermaphrodite have been made. Hooks[2] has given a splendid review of the literature dealing with sex determination, sex differentiation, and the effects of hormones on sex. It would be superfluous to further discuss this subject here.

I shall now take up the treatment of intersexuality which is more particularly in our field of endeavour. I have previously advocated that this treatment should

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[1] Severinghaus, A. E.: Am. J. Anat., **70**: 73-87, 1942.
[2] Hooks, C. A.: J. Urol., **62**: 528-534, 1949.

FIG. 6

begin on the day of the birth of any individual whose sex is in doubt.[3] It is unfortunate that at the present time the only method by which gonadal sex can be determined is by exploration and biopsy of the gonads. As far as determining the gonadal sex is concerned, no cystoscopic, endoscopic or x-ray study is of any value whatsoever. Coffey did uretero-intestinal anastomoses on new-born babies in cases of exstrophy of the bladder. Babies are accustomed to anoxia and stand operation well. There is therefore no reason why an intersex baby should not be explored immediately at birth, and there is every reason why it should be because of the havoc which such an individual brings to a family. If, upon exploration, the baby is found to have ovaries, the clitoris should be amputated at once and the mother told that she has a girl baby. If testicles are found the mother should be told that she has a boy who has hypospadias that can be cured when he is 4 years old. There is no place in the world for an intersex individual. The sensational accounts appearing in the newspapers of today of girls being changed into boys and boys into girls are not tributes to modern medical science but a terrible indictment of the medical profession who did not make this determination when it should have been made: on the day of birth of the individual.

It can be seen from the case which I have presented the tremendous influence of psychic sex. This patient was unquestionably predominantly a gonadal female and, I believe, a genetic female, but because the individual had been raised as a boy, everything else to the contrary, he insisted upon living the life of a boy and being surgically constructed into a male. Psychic sex is something not to wait for but to be developed; all the more important is it that the gonadal sex should be determined at the earliest possible date. I am not, however, advocating the change of psychic sex of an individual on gonadal findings alone later in life.

The case which I have reported brings out an important surgical procedure which I have previously described.[4] In 1949 Howard[5] published an article in which he pointed out the high degree of feminism in cases of hypospadias where the urethra opened in the perineum, and that these cases showed a vagina, uterus and tubes. It occurred to me, therefore, that since I had cured many cases of perineal hypospadias in which a vagina was present but unknown to me, that in the case which I have presented it would not be necessary to remove the vagina as had previously been advocated in such cases. I therefore constructed the terminal urethra as I have described, and anastomosed the urogenital sinus with the urethra. The vagina has given no evidence of its presence. I am therefore convinced that it is surgically proper not to remove the vagina in intersex individuals where male construction is to be carried out.

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[3] Cecil, A. B.: Discussion. Trans. West. Sec. A.U.A., p. 125, 1950.
[4] Cecil, A. B.: J. Urol., 62: 709–712, 1949.
[5] Howard, F. S.. Surg., Gynec. & Obst., 86: 307, 1948.

ADDENDUM

Since presenting this paper, Moore, Graham and Barr have described a method for the detection of chromosomal sex by a skin biopsy (Surg., Gynec. & Obst., **96**: 641, 1953).

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UROLOGICAL PROBLEMS IN AGENESIS OF ABDOMINAL WALL MUSCULATURE

P. PAUL RIPARETTI AND DONALD A. CHARNOCK

This paper presents the urological abnormalities associated with agenesis of the musculature of the abdominal wall. Recognition of this syndrome dates back to the turn of the century but it has not been until recent years that improved diagnostic and surgical techniques have made possible the treatment of these patients. Sixty-one cases have been reported, to which we add five.

This syndrome consists of two basic findings: 1) Partial to complete absence of the abdominal wall musculature, 2) abnormalities of the urinary tract, which usually presents enlarged and hypertrophied bladder, hydrourethers and hydronephrosis. Patent urachus, obstructions at the vesical neck and atresia of the urethra have been noted. Other common anomalies are cryptorchidism, malrotation of the intestines, megacolon, spina bifida, pigeon chest and some form of talipes (Eagle and Barrett; Silverman and Haang).

The syndrome occurs predominately in males. Of the cases reported, only three have been observed in females. The mortality rate has been high, most of the deaths occurring in infancy from pneumonia, pyelonephritis, bacteremia and uremia.

Two principal theories have been advanced to explain the pathogenesis of this condition. Osler reported a case in 1901 which he had seen in 1897. In his characteristic way, he had sought the advice of Dr. C. R. Bardeen, then associated with the Department of Anatomy of the Johns Hopkins Hospital. Bardeen suggested that the lack of resistance normally met with in the abdominal wall might allow the bladder to expand rather than to empty secretions into the amniotic cavity. He though this might be due to faulty development of the blood supply.

Stumme in 1903, postulated that obstruction at, or distal to, the bladder neck, early in fetal life, resulted in dilatation of the bladder and involvement of the ureters and kidneys. The enlarging urinary system caused atrophy of the abdominal wall musculature, either by direct pressure or by diminishing its blood

In our opinion, the theory of Stumme is the more logical, but neither theory adequately explains the problem. While over half the cases reported had bladder neck obstruction, several, including two of our own, showed obstruction at a higher level. Moreover, many infants with dilated bladders due to bladder neck obstruction have no abnormality of the abdominal musculature.

The diagnosis of this syndrome usually does not present any great problem. The condition is readily recognized by the obstetrician or the pediatrician. Upon examination of the infant, the abdominal skin is usually wrinkled and looks like the skin of a dried prune. The underlying abdominal viscera may easily be seen beneath the skin of the thin abdominal wall and the various organs readily palpated. If the infant is placed on his side the abdominal viscera fall to the dependent portion and if placed flat on his back, the flanks bulge. As most of these cases are males, bilateral cryptorchidism is usually present.

Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953.

In studying these unfortunate infants a thorough urological examination is imperative. A nonprotein nitrogen determination is obtained which serves as a base line for future comparison of the patient's progress. The residual urine should be determined and a cystogram done. We prefer the delayed cystograms as described by Stewart since a reflux up the ureters may outline the upper tract, thereby eliminating the necessity of retrograde examination (Stumme). Cystoscopy should be done early and one must search the bladder neck very carefully for any evidence of obstruction in this suspected area. If the nonprotein nitrogen is within reasonable limits, excretory urography using delayed 1, 2 and 3 hour films is valuable. Some of our best urograms were made 3 hours after the intravenous injection of the iodide solution. It goes without saying, that the pediatrician and the urologist should work together in the treatment of these infants.

CASE REPORTS

Case 1: Baby P.M., aged 3 weeks, was admitted to the Childrens Hospital on September 28, 1948. The infant was a full term baby, weighing 7 pounds, 5 ounces at birth. No complications occurred during delivery and no prenatal complications developed. At birth, the obstetrician noted the absence of the anterior abdominal wall musculature.

Examination of the abdomen revealed bulging of the flanks (fig. 1, *A*). The intestinal pattern could easily be seen beneath the anterior abdominal wall. No abdominal muscles were palpated. The bladder was firm and distended. Bilateral cryptorchidism was present.

The hemoglobin was 141 per cent. The white blood cell count was 21,900. The urine showed 1 to 2 plus albumin and was loaded with white blood cells. The nonprotein nitrogen was 65 mg. per cent and rose to 160 mg. per cent. The CO_2 combining power was 17 volumes per cent. A cystogram revealed bilateral hydro-urether (fig. 1, *B*). A No. 6 ureteral catheter was passed into the bladder and 10 cc of cloudy urine obtained. The bladder remained distended.

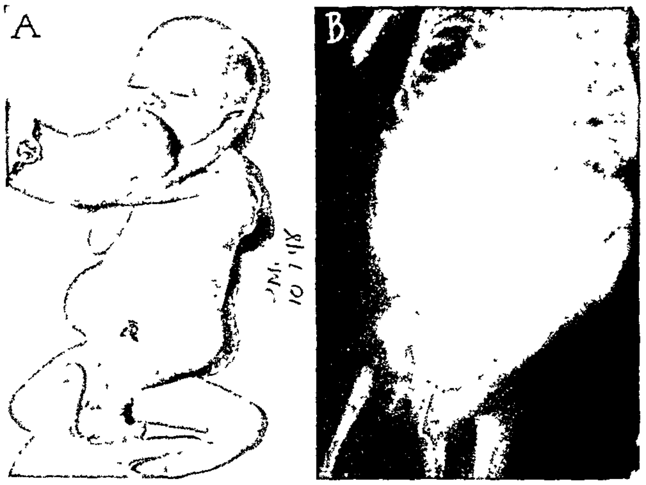

FIG. 1. Case 1. *A*, note bulging of flanks and distended bladder. *B*, delayed cystogram showing dilated ureters.

The baby did poorly from the onset, refusing his formula and vomiting. Dehydration progressed and acidosis increased. The nonprotein nitrogen continued to rise and the infant expired on October 14, 1948.

Autopsy findings were confined to the abdominal wall and genito-urinary systems. There was no evidence of muscles in the ordinary sense of the word. A few fibers of the internal and the external oblique were seen. No recti fibers were found. The abdominal organs were in their normal anatomical position. The right kidney weighed 5 gm. and the left kidney 10 gm. The pelves were dilated and contained a large amount of thick yellow fluid. There was an extreme thinning of the cortex. The pelvic mucosa was thickened and injected. On the right side, an obstruction was found in the ureter about 1 cm. proximal to the bladder and consisted of a fibrous thickening for a distance of 2 mm. The left ureter was tremendously hypertrophied, measuring 1 cm. in thickness and was very firm. There was marked thickening of the bladder wall. The mucosa of the bladder appeared to have minimal trabeculations. No bladder neck obstruction was apparent. On opening the urethra, no obstruction was noted. The right testicle was felt along the course of the right ureter and the left testicle was not located.

Microscopic findings of the kidneys showed the tubules and the glomeruli to be destroyed and in many places replaced by connective tissue. Clumps of bacteria were seen in the tubules. The ureters showed thickened fibrous walls. The bladder wall musculature showed thickening with increase in the size and the number of fibers.

Case 2. Baby S. R., aged 2 weeks, was admitted to the Childrens Hospital on April 14, 1949. Birth weight was 7 pounds, 10 ounces. The baby was said to have been strong and healthy at birth, but on the third day he became feverish and refused to eat. The parents were told at the time of birth of the abdominal wall abnormality and the possibility of associated genito-urinary abnormalities.

Physical examination revealed a small, malnourished infant in severe dehydration with complete absence of the anterior abdominal wall musculature and with marked wrinkling of the anterior abdominal skin. The kidneys were palpable in their normal position. There was bilateral cryptorchidism and a moderate degree of phimosis.

Laboratory results showed a hemoglobin of 16.6 gm. and a white blood cell count of 34,400. The nonprotein nitrogen was 91 mg. per cent and it rose to 122 mg. per cent a few days later. A blood Kahn and Kline were negative. Several urine examinations were done and all showed 4 plus albumin and were loaded with white blood cells. Culture of the urine revealed hemolytic staphylococcus aureus.

Nos. 10 and 12 sounds were passed through the urethra with some difficulty. It was felt at that time that there was a bladder neck obstruction or that there was a valve in the posterior urethra. Cystogram revealed bilateral hydro-ureter and enlarged smooth bladder. The infant did poorly, failed to respond to antibiotics and died on the sixteenth hospital day.

Autopsy showed a complete absence of the musculature of the anterior abdominal wall. The skin was thrown into wrinkles and folds. The intestinal pattern and shape of the various underlying organs was outlined against the skin of the abdomen. All of the abdominal organs were easily palpated. The right kidney weighed 35 gm. Both kidneys showed a moderate amount of fetal lobulation. The left kidney was markedly hypoplastic. Upon opening the kidneys the calyces were found to be filled with infected urine. There was a marked degree of hydronephrosis. Both ureters were markedly dilated and tortuous throughout their entire course and resembled small bowel in gross appearance. No apparent obstruction was found at the ureterovesical or the ureteropelvic juncture. The bladder wall was thickened but there was no evidence of sacculation or trabeculation. Both testes were found at the pelvic brim. No bladder neck or urethral obstruction was detected.

Case 3. Baby M. N., aged 36 hours, was admitted to the Childrens Hospital on February 2, 1950. The obstetrician noted a complete absence of the anterior abdominal musculature and the infant was sent to this hospital for urologic evaluation.

Physical examination demonstrated a flaring-out of the lower thoracic cage (fig. 2, *A*). The abdomen showed marked wrinkling of the anterior abdominal wall and there was complete absence of the musculature in this area. There was a patent urachus located approximately 2 cm. below the umbilicus in the midline. Urine was draining from this area. The bladder could be percussed up to this point. The abdominal organs could easily be felt through the abdominal wall. Both kidneys were palpable. Bilateral clubbed feet were present.

Laboratory results showed a hemoglobin of 23.6 gm., 152 per cent. Platelets were normal. The white blood cell count was 11,400. The urine showed 4 plus albumin with many white blood cells. The nonprotein nitrogen on admission, was 48 mg. per cent.

The color was good. The respirations were normal and the infant was quite active. Some urine was seen to come out of the penis but most of the time the urine drained from the patent urachus. A No. 5 ureteral catheter was easily introduced into the orifice of the patent urachus and a cystogram was done (fig. 2,

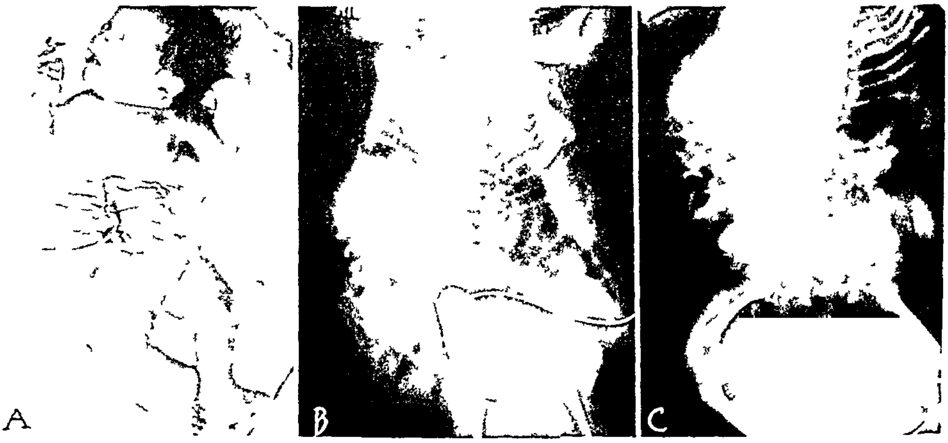

FIG 2 Case 3. *A*, wrinkling of abdomen and deformity of feet *B*, cystogram done through patent urachus with No 6 ureteral catheter Note deformity of rib cage. *C*, 3 hour delayed excretory urogram, showing dilated ureters.

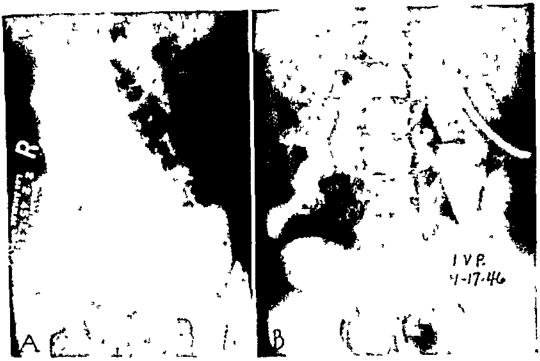

FIG. 3. Case 4. A, cystogram showing marked deformity of bladder. B, bilateral nephrostomy and urethral catheter. Dilated and angulated ureters.

B). The bladder outline indicated enlarged hypertrophied bladder with a rather smooth wall. There was no reflux of the dye into the ureters and the kidneys. On February 12, 1950, an excretory urogram was done. Prompt excretion of the dye occurred in both kidney pelves and in the right ureter. In the 2-hour film, both ureters an both kidneys were well visualized. The ureters were extremely tortuous and the pelves were markedly dilated. The calyces were not outlined (fig. 2, C).

A suprapubic cystotomy was done and the infant was discharged and has been followed in the clinic. His general condition is good.

Case 4. R. H., aged 17 years, was first admitted to the Childrens Hospital at the age of 12 years. The past history revealed that he was another example of agenesis of the anterior wall musculature with urinary tract abnormalities. He had his first attack of pyuria in 1937. He was treated with sulfa drugs available at that time and his symptoms disappeared. An abdominal support was fitted which he has worn faithfully since then. He had recurrences of chills, fever, and pyuria during the intervening years.

On physical examination the chief findings were related to the abdominal wall and genito-urinary systems. Complete agenesis of the anterior abdominal muscles was present; the bladder could be palpated up to the umbilicus. Neither kidney could be felt. The testicles were not in the scrotum. A catheter was passed into the bladder without undue difficulty and purulent urine was obtained.

Laboratory tests showed a hemoglobin of 81 per cent, white blood cell count of 16,000, the nonprotein nitrogen was 31 mg. per cent, and the urine showed 1 plus albumin with many white blood cells. The urine culture produced E. coli. Cystogram reveled a smooth, large bladder (fig. 3, A). An excretory urogram revealed bilateral hydro-ureter and hydronephrosis (fig. 3, B). In February 1945, cystoscopy showed no evidence of bladder neck obstruction or valve formation. The ureteral orifices could not be localized due to the generalized inflammation of the bladder wall. A urethral catheter was left in place for drainage. In March, 1945, a left nephrostomy was performed. The kidney showed hydro-ureter and hydronephrosis with marked thinning of the kidney parenchyma. On May 1945, a right nephrostomy was done. In each of the incisions only an occasional fiber of the internal and the external oblique were encountered. In 1947, the left ureter was explored and was re-implanted into the bladder for better drainage. At the time of the left partial ureterectomy and re-implantation of the ureter into the bladder a cystotomy was also done. At the present time his bladder is quite decompensated. He is being maintained on cystotomy drainage. Both nephrostomy tubes have been removed. He wears an abdominal support and carries on routine activities. The general mental and physical condition of this boy has been satisfactory. He is now 20 years old and is attending college.

Case 5. M. S., aged 3½ years, a Negro, has had multiple hospital admissions at the Santa Barbara County and the Cottage Hospitals, for upper respiratory and urinary tract infections. At birth it was noted that he had agenesis of the abdominal wall musculature and the parents were told of the possibility of genito-urinary disease. He began to walk at 18 months and has worn an abdominal corset since 1 year of age. On physical examination, the chief findings were a prominence of the bony sternum with a depressed ensiform process (fig. 4, *B* and *C*). Partial to complete absence of the anterior abdominal wall musculature was present and prolapse of the abdominal contents. During his many hospital admissions, his urine has shown infection. The nonprotein nitrogen has varied from normal to 60 mg. per cent. He has bilateral cryptorchidism.

In April 1952, excretory urography disclosed some dye in the left kidney region, but no dye was in either kidneys, ureters, or bladder (fig. 4, *A*). In August 1952, retrograde pyelograms were done. A No. 16 Brown-Burger cystoscope was used to visualize the bladder which was seen to be smooth, without trabeculation, and both ureteral orifices were patulous. The bladder neck was carefully visualized

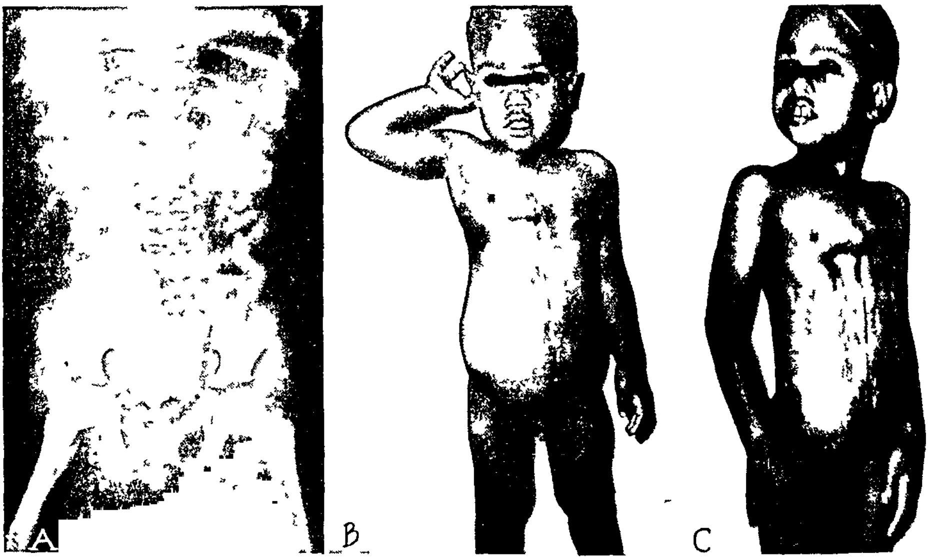

FIG. 4. Case 5 *A*, delayed cystogram showing reflux of dye and hydro-ureters and hydronephrosis. *B*, first operative procedure. Note bulging of right abdomen. *C*, postoperative condition. Illustrates improved abdominal support. (Photographs in *B* and *C*, courtesy of Dr Kathryn L. Stephenson.)

and there was no evidence of obstruction in this area. The residual urine was checked at various times. This varied from 0 to 100 cc.

A plastic surgeon, Dr. Kathryn L. Stephenson, became interested in the patient and it was decided that a different approach should be taken to try to correct the genito-urinary changes. Three operative procedures were undertaken to strengthen the abdominal walls. At the first operation a thin graft was taken from the abdomen with a dermatome. It was elliptical in shape and extended from the pubis to sternum. The adjacent skin and subcutaneous issues were undermined and superimposed to the midline. At the second operation, this procedure was repeated more laterally on the right and also on the left side. Following thickening of the abdominal wall, additional support was given in a third operation by the use of homogenous fascial transplants from the ribs to iliac crest, from the pubis to the sternum and from the iliac crest to the ribs on the opposite side.

The purpose of the grafts were twofold; to facilitate defecation and urination and to prevent the increasing chest deformity by counter traction on the rib cage. Between operations he wears abdominal support, is up and around and is in fairly good health. His urine, at times, is infected. This is controlled with specific antibiotic therapy. He voids with a fairly good stream. It is too early to evaluate this interesting approach to the problem but further follow-up will be forthcoming. This case may give an index of the role of the abdominal musculature in the emptying of the bladder.

The treatment of these cases will tax the ingenuity of the urological surgeon. In general it may be divided into three phases: 1) obtaining adequate urinary drainage; 2) specific antibiotic therapy; 3) abdominal support.

It is of primary importance to obtain adequate urinary drainage in order that the kidney parenchyma may be conserved. The methods for obtaining this varies with each patient and there is no stereotyped treatment for any of these cases. Each must be treated as an individual. Each case needs adequate urological work-up.

The surgical attack on the bladder neck to relieve bladder neck obstruction, as described by Greene, is a recognized method of obtaining adequate drainage and this should be done in all cases where bladder neck obstruction is found or even suspected. This may be done transurethrally, as advocated by Nesbit and by Emmett, or by the retropubic approach, as described by Burns and by Young. Depending upon the particular situation, as demonstrated by excretory and retrograde pyelograms, the ureterovesical or ureteropelvic juncture may have to be treated. Emergency nephrostomy may be necessary to get the infant into proper condition for further surgical procedures. It must be remembered that each case is an individual problem and should be handled as such.

It is important to support the abdomen of these children. This not only gives them a sense of safety but it facilitates urination and defecation. Abdominal corsets of various types may be used.

The treatment of the urinary tract infection is important and specific treatment should be given to these patients.

The approach to the problem by an attempt to make an anterior abdominal the presence of an obstructive lesion or a urinary tract calculus had been excluded. Cultures of the urine were obtained in 40 cases prior to starting therapy. The urine culture was inadvertently omitted in 10 cases, but they were included in the study because of the evidence of bacterial infection that was present in the stained sediment. Although the specific effect of Furadantin could not be determined in this group of patients, they were evaluated from the standpoint of changes produced in the bacterial content of the urinary sediment as well as symptomatic improvement. The results of this study were divided into the following three groups: Laboratory cures, clinical improvement and failures. The laboratory cures were determined on the basis of negative cultures or an absence of bacteria and leukocytes on the gram stained urinary sediment. The cases that were considered clinically improved were free of symptoms of urinary infection, but the urine contained bacteria and leukocytes. The patients who continued to have symptoms and show laboratory evidence of urinary infection were designated as failures after 14 days of treatment with Furadantin.

Table 1 shows the type of micro-organisms found in the urine of the 50 patients included in this study and the response of these organisms to Furadantin. Until specific identification of the coliform bacilli was requested, the laboratory reported Escherichia coli, intermediate coliform, and Aerobacter aerogenes as coliforms. A laboratory cure was obtained in eight of the ten cases in this group identified as coliform bacilli. In the remaining 21 cases, 11 of the 14 cases of E. coli and three of the 5 cases of Aerobacter aerogenes responded well to Furadantin. The 2 cases of intermediate coliform bacilli were resistant to Furadantin. There were 3 cases of mixed infections. In two of these cases the mixed infection was caused by Proteus organisms and Streptococcus fecalis and in one case by Pseudomonas and Micrococcus pyogenes. Although no laboratory cures were obtained in this group, two of the 3 cases showed clinical improvement. In 10 cases the organism was identified as either a gram negative bacillus

TABLE 1. *Micro-organisms treated with Furadantin*

ORGANISM	NUMBER OF CASES	LABORATORY CURE	
		Yes	No
Escherichia coli	14	11	3
* Coliform	10	8	2
Intermediate coliform	2	0	2
Aerobacter aerogenes	5	3	2
Pseudomonas aeruginosa	3	1	2
Gram negative bacilli	9	4	5
Gram positive cocci	1	1	0
Proteus vulgaris and Streptococcus fecalis	2	0	2
Pseudomonas aeruginosa with Micrococcus pyogenes	1	0	1
Amicrobic pyuria	3	2	1
Totals	50	30	20

* Coliform includes E. coli, Aerobacter aerogenes, and intermediate coliforms.

or a gram positive coccus. A laboratory cure was obtained in 5 of the 10 cases. A negative culture was obtained after treatment in one of the 3 cases of Pseudomonas aeruginosa. Three cases of amicrobic pyuria were included in this study and in 2 cases the urine was free of pus cells after a course of treatment with Furadantin. Nineteen of the patients used in this study had chronic infections of the urinary tract and had been unsuccessfully treated with sulfonamides and antibiotic agents. Furadantin effected a laboratory cure in six of these patients and clinical improvement in five when under active treatment.

TOXICITY

Eight patients experienced nausea and two vomited while receiving Furadantin. It was necessary to discontinue the drug in 4 patients. In the remaining 6 cases, the nausea subsided after instructing the patients to take the medication after meals. There were no instances of allergic skin reactions or anemia noted in the entire group of patients treated with Furadantin.

CONCLUSION

Furadantin is an effective drug in the treatment of urinary infection caused by Escherichia coli and Aerobacter aerogenes. It may be useful in patients who have manifested allergic reactions to the sulfonamides and in instances where antibiotics have not successfully controlled the infection. Several patients experienced clinical improvement while receiving Furadantin, although the urine cultures continued to show the presence of bacteria. Furadantin was found to be ineffective in mixed infections. We could not evaluate the effectiveness of Furadantin in cases of urinary infection caused by Proteus vulgaris based upon its use in 2 cases, but other investigators have found it to be an effective agent against this micro-organism. While this series is small and does not contain an adequate representation of the type of bacteria found in urinary tract infections, it is our impression that Furadantin is a valuable adjunct to the already available chemotherapeutic and antibiotic agents. We are aware of the shortcomings in the method by which this study was carried out from a laboratory standpoint. However, the results obtained enabled us to gain a general clinical impression of the effectiveness of Furadantin which in turn should encourage more detailed studies.

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THIOSULFIL IN URINARY TRACT INFECTION

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For the treatment of urinary tract infections, a new member of the sulfonamide family is available to the American medical profession. This drug has been used extensively in Europe for the last 12 years[1, 2, 3, 4, 5, 6, 7, 8] and in the past year it has found wide acceptance in Canada.

Its chemical, pharmacological and antibacteriological properties, when compared with other sulfa drugs now in use, merit serious consideration.

Of major interest are comparisons of 1) percentage of acetylation, 2) solubility in urine in a wide Ph range, 3) incidence of systemic reaction, 4) rates of absorption from the intestine and excretion by the kidneys and 5) antibacterial spectrum and effect.

The structural formula is depicted in figure 1.

The low acetylation is probably related to the stability of the drug with strong bonding of the H atoms. The location and availability of the N radicals effects its chemical behavior. See figure 2. When giving a sulfa drug the liver converts a portion of the drug by adding the $Ch_3C=O$. In effect the blood stream contains two drugs with differing properties, the undesirable reactions caused by the acetylated form.

There are variations in the degree to which different sulfonamides are acetylated as well as individual variations in acetylation of a given sulfonamide (fig. 3). The ranges of acetylation are shown as reported.[9]

Comparative solutility in the urine of the unacetylated forms is charted in figure 4.[9, 10]

Comparative solubilities in the urine of the acetylated forms are charted in figure 5. [9, 10]

Figure 6 depicts the incidence of hematuria after the administration of various sulfonamides. The low incidence of hematuria on the administration of Thiosulfil is probably related to the high solubility of both the acetylated and unacetylated forms with the practical absence of crystaluria even in the presence of restricted fluid intake.[11, 12]

Thiosulfil is seen to be rapidly absorbed and excreted, proper blood levels may be obtained by appropriate dosage (fig. 7.).[9, 11]

Figure 8 depicts inhibition of growth of Ps. aeruginosa in vitro in urine with varying concentrations of various sulfonamides.[10]

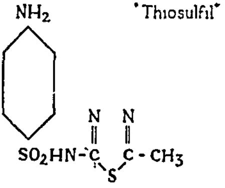
Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27-30, 1953.

[1] Schmith, K. and Reymann, F.: Nordish Medicin, **8:** 2500, 1940.
[2] Jensen, K. A. and Lundquist, F.: Dansh. Tidsskr. f. Farm., **14:** 208, 1940.
[3] Von Kennel, J. and Kimmig, J.: Klin. Wchnschr., **20:** 2, 1941.
[4] Jensen, K. A. and Possing, B.: Dansh. Tidsskr. f. Farm., **15:** 191, 1941.
[5] Jensen, K. A. and Thornsteinsson, T.: Dansh. Tidsskr. f. Farm., **15:** 41, 1941.
[6] Anderson, T. T., Schmith, K. and Sobye, P.: Ungeskr f. Laeger, **104:** 215, 1942.
[7] Frisk, A. R.: Svenska lak.-tidning, p. 1094, 1942.
[8] Alm, I. L.: Svenska lak. tidning, p. 1085, 1942.
[9] Sveck, F. A., Rhoads, P. S. and Rohr, J. H.: Arch. Int. Med., **85:** 83, 1950.
[10] Unpublished data; original research, Hall and Mckonky, March 25, 1953.
[11] Nissen, N. I. and Kadhauge, K. S.: Acta med. scandinav., **113:** 395, 1943.
[12] Nissen, N. I., Aggaard, K. and Flindt-Hansen, E.: Ungeskr. f. Laeger, **112:** 295, 1950.

The inhibition of growth of P. vulgaris in vitro in urine with varying concentration of various sulfonamides is charted in figure 9.

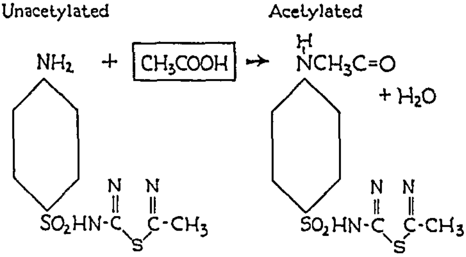
Clinical use during the past year has consisted of the treatment of 100 patients with urinary tract infection. No unpleasant or harmful reactions were encountered.

Nine patients (with urinary tract infection) who were sensitive to all other



2-Sulfanilamido-5-methyl-1,3,4 thiodiazole
(Europe 'Lucosil','Urolucosil')

Fig. 1



Solubility in H_2O at pH 7:

THIOSULFIL	9 78 gm/100cc
SULFADIAZINE	0 04 gm "

Fig 2

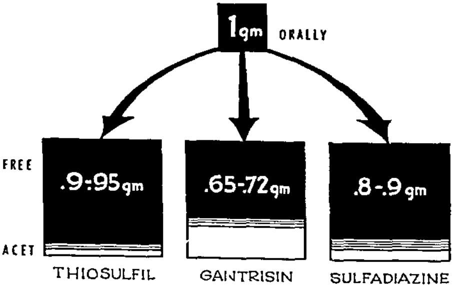


Fig. 3

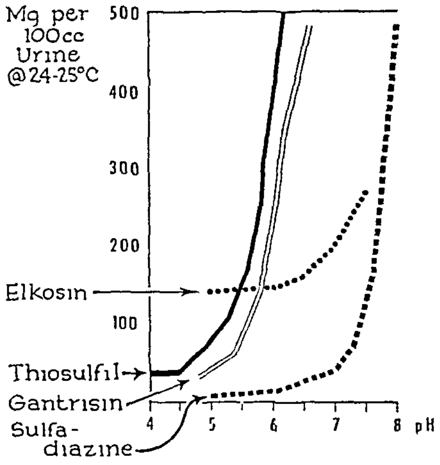


FIG. 4

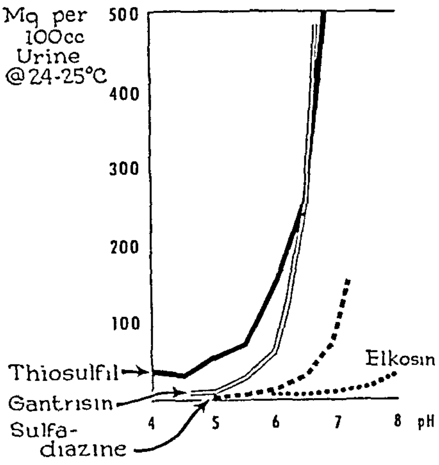
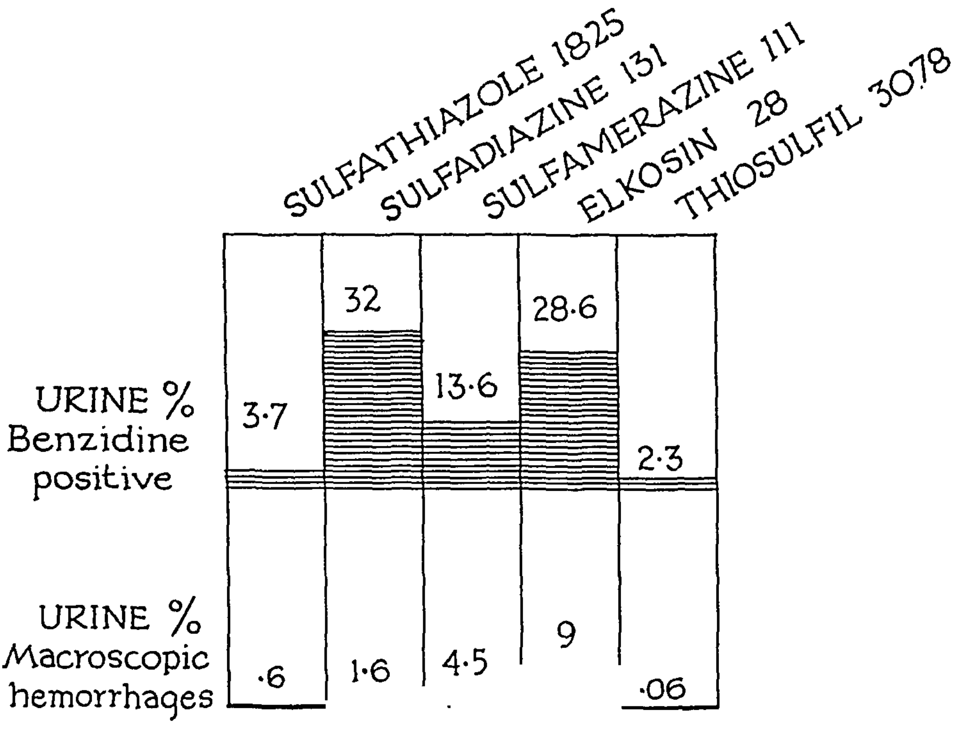


FIG. 5

sulfonamides, some in severe degree, all tolerated therapeutic doses of Thiosulfil with cure of their infection.

Thirty-one patients with mixed infections, many of whose infections had refused to respond to various sulfa drugs and antibiotics and who on complete genito-urinary survey. including cystoscopy and pyelography, demonstrated no genito-urinary anomaly, were studied. In this series a cure rate of 70 per cent



Nissen et al
1950

FIG. 6

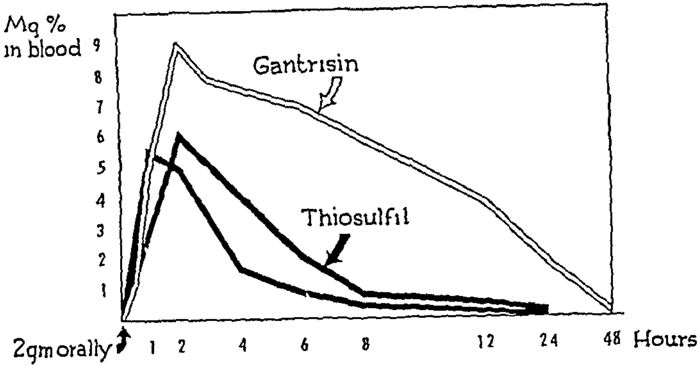
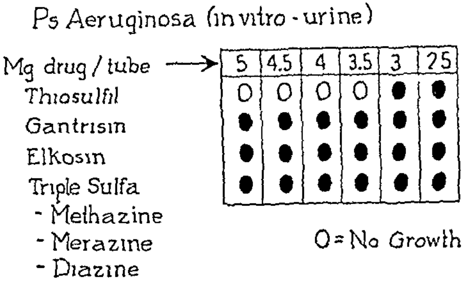


FIG. 7

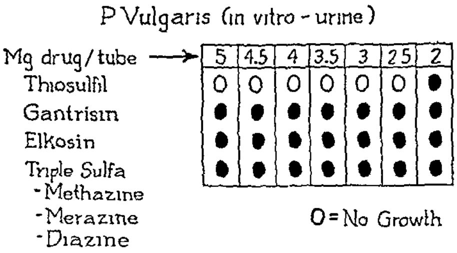


Ps Aeruginosa (in vitro - urine)

Mg drug / tube	5	4.5	4	3.5	3	2.5
Thiosulfil	O	O	O	O	●	●
Gantrisin	●	●	●	●	●	●
Elkosin	●	●	●	●	●	●
Triple Sulfa - Methazine - Merazine - Diazine	●	●	●	●	●	●

O = No Growth

FIG. 8



P Vulgaris (in vitro - urine)

Mg drug / tube	5	4.5	4	3.5	3	2.5	2
Thiosulfil	O	O	O	O	O	O	●
Gantrisin	●	●	●	●	●	●	●
Elkosin	●	●	●	●	●	●	●
Triple Sulfa - Methazine - Merazine - Diazine	●	●	●	●	●	●	●

O = No Growth

FIG. 9

was obtained, 4 per cent showed no improvement and 26 per cent showed moderate to marked improvement.

Mrs. S. H. aged 24, a nurse, was seen on May 25, 1953 in consultation complaining of hematuria with severe right renal and abdominal pain requiring morphine for relief. Excretory urograms demonstrated right hydronephrosis with decreased kidney function and right ureteropelvic junction obstruction. Her temperature was 101.8F. The urine contained many white blood cells and red blood cells. On gram stain the urine contained short gram negative bacilli. The patient had been under treatment for the previous 3 months with rather poor results inasmuch she was found to be sensitive to all sulfa drugs and most of the antibiotics.

Thiosulfil, .5 gm. was given every 4 hours. In 36 hours the temperature was normal with no evidence of drug sensitivity and the patient was free of pain. In 10 days urine studies were negative. Split renal studies and retrograde pyelograms demonstrated marked recovery of right kidney function.

SUMMARY

A new member of the sulfonamide family is available. I have studied its use in Europe with increasing interest in the past 3 years and have had the opportunity to give it 1 year's controlled clinical trial. Its chemical, pharmacological and antibacteriological properties are compared to other members of the sulfonamide family in present favor.

Clinical trial appears to indicate that the drug can be tolerated where other sulfa drugs cannot and that it is effective where some others are not. An attempt has been made to discover and explain why this is true.

CONCLUSION

Thiosulfil has an extremely low rate of acetylation.

It is highly soluble in urine over a wide Ph range in both the unacetylated and acetylated form.

There is a low incidence of systemic reaction.

The rate of absorption from the intestine and excretion by the kidneys is high.

It has an antibacterial spectrum and effect which compares favorably with other members of the sulfa family.

I believe that Thiosulfil deserves wide clinical acceptance.

ADDENDUM

During the year since this study was reported, additional clinical information has been obtained. Thiosulfil has now been under trial and observation in my practice for 30 months.

It has been necessary to interrupt treatment because of mild sensitivity consisting of loss of appetite and lassitude in one case in a series of 300 patients.

I do not hesitate to give Thiosulfil to a patient in whom there is a history of sensitivity to sulfa drugs. I have seen no cases of exanthemata, urticaria, emesis, fever, hematuria or crystaluria.

The drug has been given with good results in the presence of urinary retention and severe uremia. At my suggestion it was given with good results to control a secondarily infected eczema on the hands of a 7-year old boy with severe, acute nephritis and sensitivity to antibiotics.

Early experiments in rats indicate that large amounts of Thiosulfil can be placed in the abdominal cavity without subsequent evidence of peritoneal irritation; 50 mg. were placed in the abdominal cavity of rats weighing 180 gm., the equivalent of 25 gm. in the abdomen of a man weighing 90 kilograms.

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RESULTS IN ARTIFICIAL INSEMINATION

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Contrary to usual belief, human artificial insemination has been practiced in the United States for nearly 100 years and its use is steadily increasing

The first inseminations in this country were performed by J Marion Sims[1] in 1866, who inseminated six women artificially a total of 55 times, with one resulting pregnancy, which terminated in a spontaneous abortion

In the ensuing years, very little insemination was attempted, Rohleder,[2] in 1924, was only able to collect 127 cases with 52 pregnancies Engleman,[3] in 1928, brought the series up to 185 cases with 65 pregnancies

This report will consist of a comparison of results of AID using two different methods of insemination

With the first method, the semen is instilled onto the cervix with a Cary cannula The second method uses a relatively tight-fitting plastic cup, first described by Whitelaw [4]

In either case, the indications for performing AID remain the same 1) The husband must be irreparably sterile 2) The wife's pelvic organs must be normal 3) The wife must have normally functioning tubes 4) She must ovulate normally in a majority of her cycles 5) Both husband and wife must equally desire this method of reproduction and both must understand the possible legal and psychological consequences

I believe that again the prerequisites for insemination should be reviewed They are as follows

1) Both wife and husband should be interviewed and the infertility of the husband determined

2) The probable fertility of the wife must be determined

3) There should be a "cooling off" period, an interval during which the couple can review the picture dispassionately and during which the physician will see both husband and wife and familiarize himself with the mental and psychological make up of the couple

4) A careful selection of the donor is paramount The donor must remain anonymous, and should never be a relative or friend of husband or wife The donor must be fertile, above average mentally and physically, with no hereditary diseases He should resemble the husband as closely as possible, racially and physically and have an Rh factor compatible with that of the wife

5) The specimens of semen should be obtained and delivered to the office as

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Read at annual meeting, Western Section of American Urological Association, San Francisco, April 27–30, 1953

[1] Sims, J M Clinical Notes on Uterine Surgery, With Special Reference to the Management of the Sterile Condition New York William Wood & Co , 1866

[2] Rohleder, H Normale, Pathologische und Kunstliche Befruchtung beim Menchen Berlin, 1924, p 204

[3] Englemann, F Klin Wehnschr 7 1563 1928

[4] Whitelaw, M J Use of the cervical cap to increase fertility in cases of oligozoospermia Fert & Steril , 1 33–39, 1950

TABLE 1

	TOTAL NUMBER	INSEMINATIONS OLD METHOD		INSEMINATIONS NEW METHOD (PLASTIC CUP)	
Cases	177	50		127	
Pregnancies	134	28		106	
% Pregnancies	75.7%	56%		83.3%	
Full-term deliveries	84				
		Preg	Not Preg	Preg	Not Preg
Inseminations	1199	213	226	567	193
Average No. Inseminations	6.81	7.6	10.28	5.34	9.19
Cycles	677	104	109	349	115
Average No Cycles	3 82	3.71	4.95	3.29	5.47

soon as possible and in such a manner as to insure no possible meeting between donor and recipient.

6) A written consent to the insemination, signed by both husband and wife, before a witness, is essential.

The timing of the insemination is based on the patient's previous menstrual records and on her basal body temperature readings. The attempt is made to inseminate on the drop in temperature, this being 14–15 days before the shortest expected period that the patient has recorded. Further inseminations are then performed, if necessary, on alternate days during the mid-cycle or on any other drop in temperature.

The new technique of performing artificial insemination is very simple. The cervix and vagina are first cleaned and dried by wiping with a cotton pledget. On the first inseminations, cervical mucus is removed for study and a sperm penetration test performed.

The semen is then placed in a plastic cup of correct size, and inserted into the vagina and over the cervix, where suction holds the cup in place. Care must be taken that none of the semen is spilled during insertion of the cup. The cup is slipped along the posterior wall of the vagina in a horizontal position, dome down, until the cervix is reached, where a slight added pressure posteriorly permits the cup to slip over the cervix. Thus the cup acts as a means of keeping the entire semen specimen in close contact with the cervical os. It is left here for 24–48 hours, when it is removed either in the office by the physician or by the patient at home. If removed in the office, an examination of the cervical mucus is done and usually myriads of active sperm are found, even though up to 48 hours have elapsed since the insertion of the semen.

In the total series, 177 women were inseminated with the semen of a selected donor, resulting in 134 pregnancies (75.7 per cent).

In the first group of 50 cases, where the Cary cannula was used, a total of 28 patients became pregnant (56 per cent). These include 36 previously reported by me[5] in 1946, plus 14 subsequent cases.

[5] Haman, J. O.: Artificial insemination. Calif. Med., 68: 353, 1948. No. 5, May, 1948

TABLE 2

Pregnancies		
Male	51	(60.71%)
Female	33	(39.29%)
Unknown	4	
Miscarried	24	(17.9%)
Undelivered	22	
No pregnancies	43	
Total	177	

The second group of 127 cases, in which the plastic cup was used, resulted in 106 pregnancies (83.3 per cent) (table 1). I have used the plastic cup exclusively since 1948.

It is interesting to note the difference in the percentage of pregnancies between the two methods—56 per cent and 83.3 per cent. It is also of importance to note that the average number of inseminations, as well as the average number of cycles required for pregnancy, was materially lowered when the plastic cup was used.

Another important feature is that no complications arose with the use of the plastic cup, whereas there were 5 complications (9.6 per cent) when the cannula was used. These complications included transient endometritis and 3 cases of acute pelvic inflammatory disease which required hospitalization, even though none of the semen was placed above the internal os.

Of the 134 pregnancies, 51 (60.7 per cent) were male infants and 33 (39.3 per cent) females. Four cases were lost because of incomplete follow-up, 24 patients miscarried and 22 remain undelivered. (table 2).

The average length of pregnancy from the day of conception to that of delivery was 267.2 days; that for males 264.7 and females 270.5.

Pregnancy followed a single insemination in 24 cases, and in 23 other cases, pregnancy followed with insemination in only one cycle, making a total of 47 patients that became pregnant in one menstrual cycle. The greatest number of inseminations performed on a patient who became pregnant was 34. Twenty-three patients received 10 or more inseminations before pregnancy occurred. There were no twins, moles or ectopic pregnancies. Two of the children were stillborn, though full term. One child was born with a hair-lip. Two patients required cesarean sections. Two patients now have had four pregnancies each, four have had three, 24 have had two by this method of insemination and the remaining 66 have had a single pregnancy.

The number of miscarriages in this series of artificial inseminations is about the same as reported for normal conceptions. Twenty-four of the 134 pregnancies miscarried (17.9 per cent). This percentage parallels the number of spontaneous abortions that might be expected in normal conceptions. Malpas[6] estimated an 18 per cent fetal loss, Whitehouse[7] 17.6 per cent, Mall[8] 20 per cent and Brunner

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[6] Malpas, P.: J. Obst. & Gynec. Brit. Emp., 45: 932, 1938.
[7] Whitehouse, B.: Proc. Roy. Soc. Med., 23: 248, 1929–30.
[8] Mall, F. P.: Am. J. Anat., 22: 49, 1917.

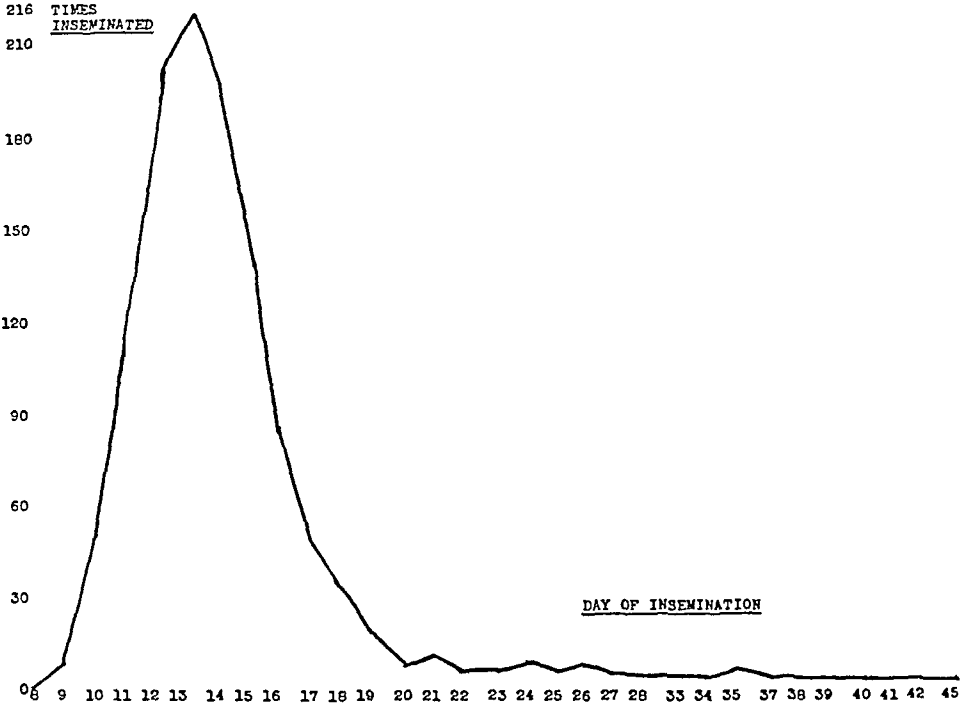

FIG. 1

and Newton[9] 15.8 per cent in their series of fertile matings, while Cary[10] reported 10.6 per cent of miscarriages in his series of 66 successful AID's.

Ovulation was considered to be between the low point in the mid-cycle and the beginning of the sustained rise which followed. Any insemination that occurred on either of these two days, or the day before the drop, was considered to have been inseminated at the time of ovulation. In the successful cases, even though insemination on ovulation day was performed 434 times, only 134 pregnancies resulted. Among those that did not become pregnant at all, 59 were inseminated 130 times on ovulation day with no success.

Seventy seven of the patients had regular cycles (varying four days or less) and of these, 64 became pregnant. Those patients whose cycles varied from 5 to 10 days, of which there were 72, had 50 pregnancies and 28 patients who had cycles varying more than 11 days showed 20 pregnancies.

A total of 63 donors were used during the series, some only once or twice, others more frequently. Only 27 of these donors were successful in impregnating these potentially fertile women, even though all of the donors were considered to be normal fertile males by our present standards. Five donors were responsible for 90 pregnacies, one donor siring 35, and another 22. There was no definite pattern of the results of the pregnancies. No one donor produced predominantly males or females and none was responsible for more than the average number of miscarriages. The other 22 donors produced the remaining 44 successes.

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[9] Brunner, E. K. and Newton, L.: Am. J. Obst. and Gynec. 38: 82, 1939.

[10] Cary, W. H.: Results of artificial insemination with an extramarital specimen (semiadoption). Am. J. Obst. & Gynec., 56: 727–732, 1948.

TABLE 3

	DAYS PREGNANCY OCCURRED												
	10	11	12	13	14	15	16	17	18	19	21	23	24
Number of Pregnancies......	2	15	18	23	26	22	13	6	4	1	2	1	1

The day of insemination varied from day 9 to day 45 of the cycle. However, 81 per cent of the inseminations were performed between days 11 and 16 (fig. 1).

The fruitful inseminations occurred most frequently on days 13, 14 and 15, these days accounting for over half of the pregnancies (table 3). No pregnancies occurred when insemination took place before the tenth day or after the twenty-fourth day (fig. 2).

The number of patients who became pregnant within three months of insemination was 90, or 67.1 per cent of the total. Twenty-four additional women, making a total of 114, were pregnant within 6 months (86.2 per cent).

There was also a difference between the two methods in this respect. Without the cup, 16, or 57.1 per cent, were pregnant in 3 months as against 74, or 69.8 per cent, when the cup was used.

No court in the U.S., Canada or Great Britain has any statutory law aimed at artificial insemination.

The legitimacy of the child is presumed, as is all issue of a legal marriage. Only proof of the strongest character, by other persons, of the utter impossibility of the child's legitimacy can overcome this presumption.

Under California laws (and those of most of the Western states), any child born of a marriage when the husband and wife are living together and the husband is not impotent, is presumed to be legitimate, and if the foregoing two

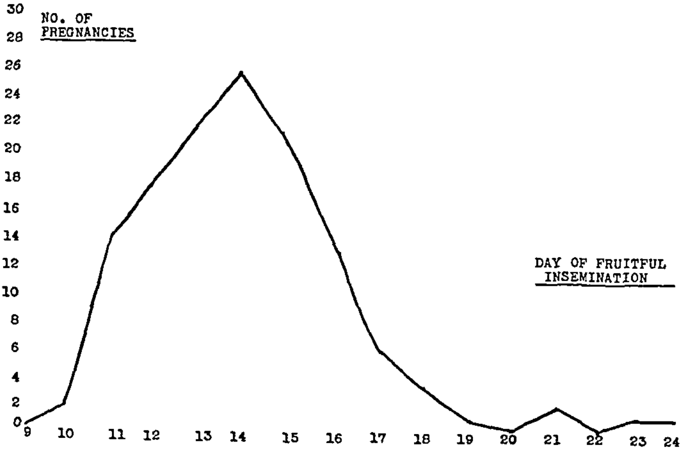

FIG. 2

conditions are met, this presumption is conclusive and indisputable (Civil Code, Sec. 194; Code of Civil Procedure, Sec. 1962(5)). However, the husband (or his descendants) has the right to offer proof that he was not cohabiting with his wife (as if he were "beyond the seas") during the time of conception or that he was impotent.

There is no agreed legal definition of this term, impotency, but several decisions involving the word seem to consider that impotency includes not only sterility but inability to copulate as well.

The suggestion has been made that adoption would solve the problem of the legitimacy of the child. Under California law (Sec. 224, Calif. Civil Code) a legitimate child cannot be adopted without the consent of both of its parents, if they are alive at the time of the adoption. Since all children born in wedlock are indisputably presumed to be legitimate, one would have the peculiar situation of the presumed parents attempting to adopt their own child. Therefore, the only natural assumption in that case would be that the husband was not the natural father of the child.

The method protecting the patients, the doctor and, more important, the potential child, is practiced in my office in the following manner:

Both husband and wife sign a consent giving permission to select a donor and to inseminate the wife, stating that they are living together as man and wife and that the husband is not impotent. Further, the couple understands that no guarantee is made that the patient will become pregnant, that she will carry to term or that there will be no malformation of the child.

This consent is signed by both husband and wife before a witness (my secretary) and is then placed in the patient's record. When the patient becomes pregnant, the consent is placed in an envelope in a safe deposit box, with the following written on the envelope, "To be destroyed without opening in the event of my death."

The donor has no opportunity to see the patient and the patient no opportunity of seeing the donor. Most specimens are brought to the office by me or by a messenger. Only the donor's number appears on the specimen bottle, and only the donor's number and date of artificial insemination is written into the history.

By using the foregoing methods, it has been possible to avoid emotional and legal complications to date. It is the most gratifying sensation in the world to see the parents bring the child to the office (a procedure that I demand) and see the expressions of pride and joy on their faces and hear from them the heartfelt gratitude to medical science that has made it possible for them to have such a wonderful child!

SUMMARY

The indications and prerequisites for insemination are reviewed.

The technique of using the plastic cup is briefly explained.

The timing of the insemination is based on the basal body temperature reading, the first insemination being performed 14–15 days before the shortest expected period.

One hundred seventy seven cases of artificial insemination where a donor's

semen was used is reported. One hundred thirty four pregnancies resulted from these inseminations (75.7 per cent).

The series is divided into two groups, those inseminated by instilling the semen onto the cervix and into the vagina, and those cases where a plastic cup was used to hold the semen against the cervix. With the old method, 56 per cent of the patients became pregnant and with the new method, 83.3 per cent of the patients were successfully inseminated.

The number of inseminations and the number of cycles necessary for pregnancy was materially reduced when the plastic cup was used.

The number of complications following inseminations was reduced to zero with the use of the cup.

Pregnancy ensued in 24 cases following a single insemination.

Thirty patients have had multiple pregnancies by artificial insemination.

The percentage of miscarriages (17.9 per cent) is about the same as expected in normal fertile matings.

Even though insemination was performed on ovulation day 564 times, only 134 pregnancies resulted (23.7 per cent).

Twenty seven of 63 donors accounted for all of the pregnancies, one donor impregnating 35 women.

Fruitful insemination occurred most frequently on days 13, 14 and 15; none before day 10 or after day 24.

Artificial insemination offers the possibility of bearing their own children to wives whose husbands are unable to produce offspring.

The use of the plastic cup is a valuable asset in artificial insemination.

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TRILENE* ANALGESIA IN UROLOGY

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The need for a safe, rapid, short analgesia devoid of the many unpleasant side effects commonly attributed to inhalation agents has long been recognized. Perhaps in no other branch of medicine except obstetrics is the need for such an agent more urgent than in Urology. The awareness of such a need prompted Dr. Young to write in his paper on self induction analgesia with nitrous oxide: "Cystoscopy, especially if prolonged for ureteral catheterization or endovesical operations, is occasionally a terrifying procedure."[1] The perception and response to painful stimuli vary with the individual and are influenced by many factors, such as age, sex, character, intelligence, apprehension or emotional state of the individual, and the nature of the disease. Emotionally stable individuals are inclined to be co-operative and show less outward reaction to pain, whereas those of excitable temperament often exhibit very violent reactions which are out of proportion to the painful stimuli. Apprehension may increase the response to pain while diversion tends to reduce or minimize this response.[2] It is this individual variation that permits us to perform most of our urologic examinations with only a local anesthetic. The use of local anesthetic agents, of which there are many, is helpful but often inadequate for extensive or difficult urologic procedures. In some instances urethral bleeding or individual sensitivity contraindicate their use. Routine use of general or spinal anesthesia for office procedures is impractical, requiring the use of cumbersome equipment and trained personnel. In addition, the hazards of general anesthesia must always be considered, and a period of prolonged recovery must be provided. These factors make it almost mandatory for such patients to be hospitalized, thus adding the burden of hospital costs and loss of income to the individual. Routine use of anodynes is often unsatisfactory and unwise, particularly in unaccompanied ambulatory patients. The constant search for an ideal anesthetic or analgesic agent led Hewer of England to investigate trichlorethylene.[3] The drug was previously used in the United States as an anesthetic agent by Stricker, Goldbladt, Warm, and Jackson in 1935.[4] The results of their study were inconclusive as is evident by a statement by the Council of Pharmacy and Chemistry of the American Medical Association in 1936 that "the case has not been completely made out" for the usefulness of the drug as a complete anesthetic agent.[5] Commercial grades of

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Read at annual meeting, Southeastern Section of American Urological Association, Havana, Cuba, March 26-29, 1953.

* Trilene (trichlorethylene) is a registered trade mark of Ayerst, McKenna and Harrison, Ltd., New York, N. Y.

[1] Young, H. H.: J. Urol., **41:** 95, 1939.

[2] Pickrell, K., Metzger, J., Wilde, N. J., Broadbent, T. R. and Edwards, B. F.: Plastic and Recon. Surg., **6:** 142, 1950.

[3] Hewer, C. L.: Brit. Med. J., **1:** 924, 1941.

[4] Stricker, C., Goldbladt, S., Warm, I. S. and Jackson, D. E.: Curr. Res. Anaesth., **14:** 68, 1935.

[5] Preliminary report of Council on Pharmacy and Chemistry, J. A. M. A., **107:** 1302, 1936.

trichlorethylene have been used in the dry cleaning industry and as a solvent for greases for many years These must not be used as an analgesic agent because of impurities which can give rise to toxic symptoms such as vomiting, vertigo, optic neuritis, and nerve palsy[6] Trilene is trichlorethylene purified and made suitable for anesthesia

CHEMISTRY

Trichlorethylene is a volatile liquid with an odor resembling chloroform Its chemical formula is $ChCl\ C\ Cl_2$ It has a specific gravity of 1 47 and a boiling range of 86 to 88 degrees C It is practically water insoluble and is not inflammable *when mixed with any portion of air at ordinary temperatures and pressure*

PHARMACOLOGY

The effects of Trilene on the central nervous system are characterized by a marked and rapid degree of analgesia which renders the drug useful for many minor procedures This is followed by loss of consciousness which is regained in a matter of seconds if low concentrations have been used This rapid return to consciousness and mental clarity permits the patient to be ambulatory and in command of all his faculties within a few minutes Its effect on blood pressure is usually negligible Cardiac arrhythmias are common when Trilene is used in high concentrations, but are uncommon when utilized in analgesic amounts Bradycardia, a precursor of cardiac arrhythmias, indicates increased vagal tone due to excessive amounts of Trilene[7] Tachypnea is also a sign of excessive vapor concentrations Bradycardia and tachypnea demand that the concentrations of vapor be reduced In contrast, simple hyperpnea reflects only the patient's response to intense stimulation Body metabolism is very slightly affected, if at all Gratifying to urologists is the absence of any demonstrable renal damage produced by this drug[7] Salivation or mucous secretions are not appreciably increased, making pre anesthetic drugs unnecessary Bleeding and clotting time are unaffected

CLINICAL USE

During the past two years we have used Trilene in over 100 selected cases, to determine the efficacy of this drug as an analgesic agent for various urologic procedures Most of these were treated as out patients in whom general anesthesia or heavy sedation was not practicable or advisable These particular patients were selected because a customarily painful or difficult procedure was anticipated In most cases, no special premedication was used We have used Trilene in performing the following procedures urethral dilatations, cystoscopy, cystoscopy and ureteral catheterization or dilatation, manipulation of ureteral calculi, ureteral meatotomy, urethral meatotomy, transurethral litholapaxy, biopsy of bladder tumor, incision and drainage of perinephric abscess, cystoscopic extraction of foreign body from bladder, removal and replacement of suprapubic mushroom catheters (See table 1)

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[6] Hewer, C L Proc Roy Soc Med , 36: 463, 1943

[7] Nowill, W K , Stephen, C R and Searles, P W Evaluation of trichlorethylene as an anesthetic and analgesic agent In publication

TABLE 1. *Urologic procedures under Trilene*

PROCEDURE	NO. CASES	AGE SPAN	RESULTS		
			Unsatisfactory*	Good	Excellent
Urethral dilatation	50	12–71	2	15	33
Diagnostic cystoscopy	20	13–74	2	4	14
Retrograde pyelography	14	10–71		5	9
Ureteral dilatation	4	34–59	1		3
Manipulation of ureteral calculi	3	21–45		1	2
Ureteral meatotomy	4	21–67		1	3
Urethral meatotomy	2	27, 44			2
Changing of suprapubic catheters	5	13–23			5
Transurethral litholapaxy	2	48, 49		1	1
Extraction of foreign body from bladder	3	50–71			3
Biopsy of bladder tumor	2	32, 54			2
Incision & drainage of perinephric abscess	1	28			1
Difficult catheterization	2	48, 68		1	1

* Unsatisfactory results were attributed to instrumentation before proper analgesia.

METHOD OF ADMINISTRATION

In all instances the drug was self-administrated with a Duke Trilene inhaler (fig. 1). The patient was instructed in the use of the inhaler, the purpose to be accomplished by its use and the correct positioning of the mask on the face. The dial indicator was set at the mark 3 so that the concentration of Trilene vapor

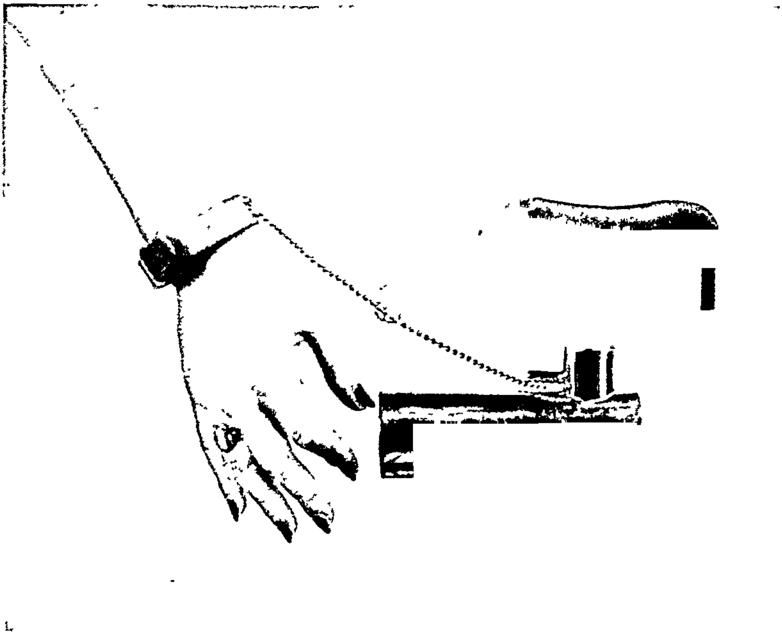

FIG. 1. Duke Trilene inhaler

received would be no greater than 0.6 volumes per cent.[8] He was allowed to take a few shallow inspirations in order to familiarize himself with the odor. He was assured he would not lose complete consciousness, but with the proper use of the inhaler, would be relieved of pain. We advised the patient to begin using the inhaler at the moment he was draped and during the interval in which we were preparing the cystoscope or other instruments for use. This allows approximately one to two minutes of inhalation prior to instrumentation. It is necessary to emphasize this point. The patient must have taken 20 to 30 inspirations before satisfactory analgesia is obtained. Painful stimulation before proper analgesia often causes the patient to become vociferous and unruly due to loss of inhibitions. Occasionally, with insufficient analgesia, a patient may exhibit a tonic contraction of extensor muscles as a result of painful stimulation. This reaction may be obviated by allowing adequate inhalation of Trilene before further instrumentation. By this routine of administration the patient is usually conscious and responsive and can co-operate throughout the procedure. If deep analgesia with loss of consciousness occurs, the hand and mask will drop away from the face allowing approximately two minutes more of painless instrumentation. By this method recovery of all cerebral functions occurs within a few minutes. These patients were checked for mental clarity by the use of simple mathematical problems and sense of direction. They were instructed to walk a straight line for sense of balance and in all instances were found to be in complete control of all faculties within a matter of five minutes or less.

OBSERVATIONS

From the physician's viewpoint, Trilene produces a rapid and marked analgesia and amnesia with minimal side effects. The simplicity and ease of administration eliminate the cost of cumbersome equipment or additional personnel. There is no excitement stage during induction. Premedication is unnecessary. The patient may be treated on an ambulatory basis and may leave the office within fifteen minutes. The occasional failures encountered have been due to improper or insufficient instructions in the use of the inhaler and hurried instrumentation before proper analgesia.

From the patient's viewpoint, Trilene has a pleasant odor. He possesses in his hands an agent to use at his discretion which will eliminate pain. It is devoid of many of the effects of other inhalation agents. It eliminates long recovery periods or possible hospitalization and generally simplifies the patient's visit to the urologist's office. The following cases and remarks are typical of the patients' responses to the use of Trilene.

M. S., aged 43, a white man, had multiple dense urethral strictures previously requiring dilatation under spinal or general anesthesia. He remarked that instruments had been passed by at least thirty different doctors and he regarded this instrumentation the easiest he had experienced. The patient has been returning at regular intervals to the clinic for urethral dilatations and each time requests the Trilene mask.

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[8] Hall, K. D., Garlington, L. N., Nowill, W. K. and Stephen, C. R.: Anesthesiology, **14**: 38, 1953.

B. S., aged 44, a white man, had two previous attempts at cystoscopy: the first under local anesthesia; the second with the use of 100 mg. Demerol and 0.1 g. sodium phenobarbital. Each time the attempted cystoscopy had to be discontinued because of pain. He has subsequently undergone cystoscopy twice, each time under Trilene and with complete freedom from pain. His reaction was that he could never have tolerated the procedure without the use of Trilene. Interestingly enough, this patient never lost consciousness, responded, and cooperated well throughout the procedures.

O. Y., aged 28, a Negress, was emaciated and debilitated from a long-standing perinephric abscess and considered by the anesthetist a poor anesthetic and operative risk. The perinephric abscess was incised and drained with breaking up of perirenal adhesions under the influence of Trilene. She complained somewhat during the procedure but had no recollection of pain after it was completed.

These are a very few typical examples of the patients' responses to the use of Trilene inhalation analgesia.

SUMMARY AND CONCLUSION

Trilene has been used in over one hundred urologic cases involving thirteen different urologic procedures with gratifying results. No alarming side effects have been observed. It possesses the following advantages:

1) Simplicity and ease of administration
2) Rapid induction and awakening
3) Marked analgesia and amnesia
4) Pleasant odor
5) Minimal side effects
6) Absence of excitement phase during induction
7) With momentary loss of consciousness, the mask falls from the face insuring maximum safety
8) Premedication, either local or systemic, is entirely unnecessary
9) Inexpensive
10) Marked assurance to the psyche

Prolonged or extensive surgical procedures do not come within the scope of Trilene analgesia and should be performed under the usual methods of surgical anesthesia.

It has been postulated that the ideal analgesic or anesthetic is one which is safe and complete and from which recovery is quick. It should be associated with minimal psychic trauma during and after induction followed by few if any side effects or complications. Trilene fulfills these qualifications as an analgesic agent.

Acknowledgment: My appreciation is expressed to W. K. Nowill and C. R. Stephen, Division of Anesthesia, Duke University for their friendly help and suggestions.

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COMMON HAZARDS OF X-RAY DIAGNOSIS IN UROLOGIC PRACTICE; THEIR RECOGNITION AND REDUCTION

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From the Department of Radiology, Parkland Memorial Hospital, Dallas, Texas

Since diagnostic x-rays are capable of causing serious injury,[1, 2] urologists should be aware of the risks involved in their use and should know how to protect patients, technicians, and themselves. Injury can be manifested by 1) anemia or leukopenia, 2) leukemia, 3) increased mutation rates, 4) fetal injury, 5) skin changes. Leukemia is reported to be nine times as frequent in radiologists as in nonradiologists.[3] The prospect of ever wider use of x-ray in Urology emphasizes the need for the urologist to utilize all safety precautions.

Total exposure during a day's work or a lifetime should be kept as low as possible, not merely below the current "maximum permissible exposure." This limit was lowered to one-half the previous value only four years ago, and it may be reduced still further in the future.

For details concerning radiation intensities about diagnostic x-ray equipment, the reader is referred to many excellent studies.[5, 6, 7, 8, 9]

Maximum permissible total body exposure is now 0.3 roentgen (r), or 300 milliroentgens (mr), per week. This is 50 mr per day for regular workers in radiation.[4] One milliroentgen is 1/1000th roentgen.

With a filter of 1.0 mm. aluminum in the primary beam, the patient's skin may receive from 0.5–1.5 r per exposure for a plain x-ray of the kidneys, ureters and bladder to 25 r for a lateral view of the pelvis. Without filter, the exposures are almost double. Scattered radiation from the patient is less intense but may be more penetrating than the primary beam. It must be remembered, however, that daily exposure to scattered radiation can result in much higher dosage to the doctor and technician than the patient receives from the primary x-ray beam at intervals separated by months or years. Measures which will reduce exposure of all concerned to reasonably low levels are simple, require little time or expense, and pay enormous benefits in safety and peace of mind.

Read at annual meeting, South Central Section of American Urological Association, Kansas City, Mo. September 21–23, 1953.

[1] Mossberg, H.: Platelet values in personnel engaged in roengten diagnostic work. Acta Radiologica, 34: 186–192, 1950.

[2] Hultberg, Sven, Larsson, Lars-Eric, and Eklund, Lennart: Some cases of radiation injury in radiologic work. Acta Radiologica, 33: 376–387, 1950.

[3] March, H. C. Leukemia in radiologists in a twenty year period. A. J. M. Sc., 220: 282-286, 1950.

[4] National Bureau of Standards Handbook 41. Medical X-Ray Protection Up to Two Million Volts. National Committee on Radiation Protection, United States Dept. of Commerce, March 30, 1949.

[5] Sorrentino, Joseph and Yalow, Rosalyn. A nomogram for dose determinations in diagnostic roentgenology. Radiology, 55: 748–753, 1950.

[6] Keane, B. E. and Spiegler, G.: Stray radiation from diagnostic x-ray beams. Brit. J. Rad., 24: 198–203, Apr., 1951.

[7] Ritter, V. W., Warren, S. R., and Pendergrass, E. P.: Roentgen doses during diagnostic procedures. Radiology, 59: 238–251, 1952.

[8] Martin, J. H.: Radiation doses received by the skin of a patient during routine diagnostic x-ray examinations. Brit. J. Rad., 20: 279–283, 1947.

[9] Trout, E. D., Kelley, J. P., and Cathey, G. A.: The use of filters to [illegible] [illegible] exposure to the patient in diagnostic roentgenology. A. J. Roent [illegible] 963, 1952.

The purpose of this paper is to point out the principal causes of overexposure to x-radiation in diagnostic Urology and to outline practical measures to reduce such hazards to a minimum. The principal dangers are from: 1) exposure to the primary x-ray beam, 2) exposure to scattered radiation from the patient, 3) unfiltered primary x-ray beam, 4) unlimited primary x-ray beam, 5) failure to employ radiation shields, 6) defective tubehead protection, 7) high MaS.-low KvP. techniques and 8) failure to measure actual radiation received.

Observation of the following principles will reduce the hazard to very low levels.

1. Never allow any part of the technician or urologist to be exposed to the primary x-ray beam unless absolutely necessary. When exposure is unavoidable, lead impregnated aprons and gloves should be worn.

2. Stay as far from the patient as possible, preferably outside the room, during actual x-ray exposures. Anyone inside the x-ray room should be behind a lead

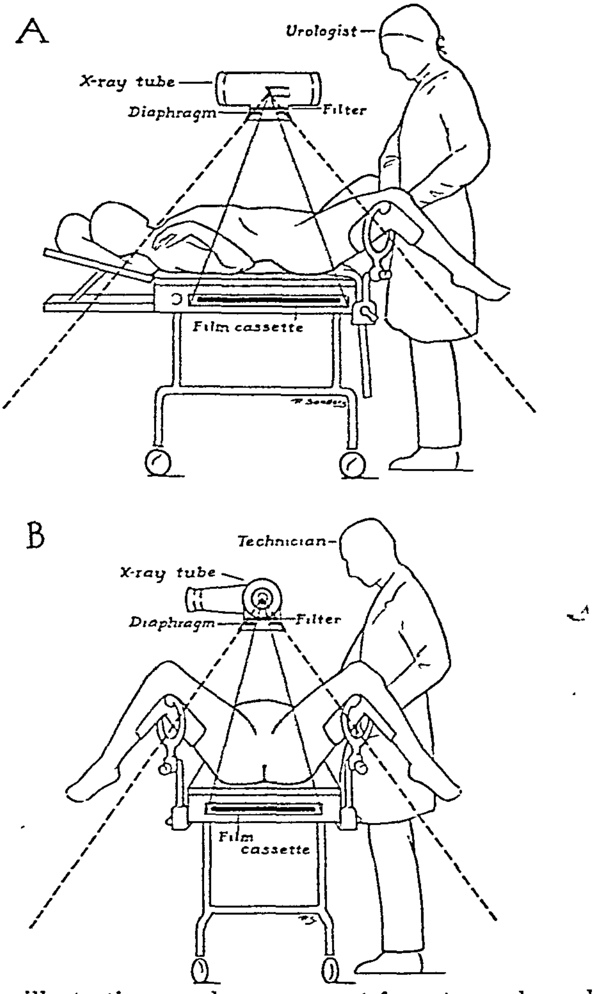

FIG. 1. *A*., diagram illustrating usual arrangement for retrograde pyelography, cystography, etc. Dotted line shows x-ray beam without diaphragm. Shaded area represents x-ray beam with diaphragm. *B*, illustrating relation of x-ray beam to technician standing beside urographic table. Dotted line shows x-ray beam without diaphragm. Shaded area represents x-ray beam with diaphragm.

protective screen. When contrast medium must be injected during the actual exposure, keep as far away as possible. If this occurs frequently, a protective apron should be worn or a screen employed.

3. Filter the primary x-ray beam with 2.0 mm. aluminum mounted permanently in the tubehead (fig. 1). This simple device reduces skin exposure to the patient about 75 per cent at medium kilovoltages, while requiring an increase of only 15–20 per cent in technique. Scattered intensities will be reduced also.

4. Limit the primary x-ray beam with a lead diaphragm (fig. 1). The beam should barely exceed the dimensions of a 14 by 17 inch film at the bucky tray level. Employ cones with smaller film sizes.

5. Stay behind a radiation shield if inside the x-ray room during an exposure. A smaller screen can be used very effectively by the urologist when he must remain nearer the patient. Never permit initiation of x-ray exposures with the bucky trip-string while standing by the x-ray table.

6. Completeness of tubehead protection against stray radiation is easily checked by surrounding the tubehead with cassettes, closing the useful aperture with lead, and making an exposure. Actual transmission in milliroentgens must be determined with a radiation survey meter.

7. High KvP.-low MaS. techniques reduce exposure to the patient compared to low KvP.-high MaS. techniques.

8. Use dental film badges routinely. This is a simple but effective objective check on the adequacy of all protective measures. It encourages safety consciousness and is definite evidence that exposure has or has not been low.

A film badge is made by fastening a lead number to the front of a dental film with adhesive tape. The badge is worn face outward on the clothing of the chest

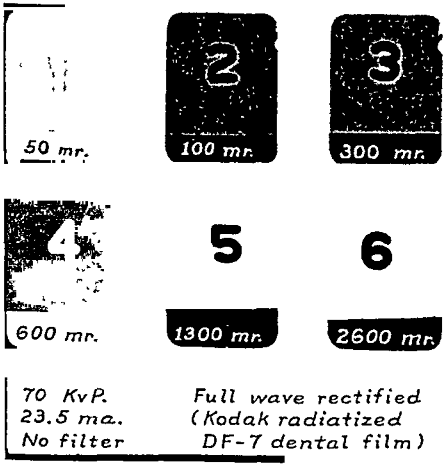

FIG. 2. Dental films exposed to various quantities of x-ray generated at factors shown

or abdomen, fastened with a safety pin. After one or two weeks, depending on volume of work done, the film is developed in regular x-ray solutions with an unexposed film as a control.

From 10 to 15 milliroentgens is required to blacken the film to a barely perceptible degree. Figure 2 illustrates dental films exposed to 50, 100, 300, 600, 1,300, and 2,600 milliroentgens. These are maximum permissible exposures for 1 day, 2 days, 1 week, 2 weeks, 1 month, and 2 months, respectively. The lower border of each film was shielded with lead and thus shows no radiation effect. The method is not quantitative except in a broad sense.[10] However, if the degree of blackening in one week or two weeks is distinctly less than that resulting from 50 mr, or one day's limit, it is obvious that exposure has been well below maximum levels. A definite medium or dark gray fog is clear warning of excessive exposure although not necessarily above maximum permissible. Defective shielding or careless violation of safety routines usually will account for the exposure.

Film badges are worn the first full work week of each month as a routine in the Department of Radiology, Parkland Hospital, Dallas, Texas by everyone working with or near x-ray machines. More than 100,000 diagnostic x-ray exposures are made per year, yet it is rare to find any perceptible exposure of a dental film.

If these safety practices are followed carefully, no harm to patients, physicians, or their assistants should occur.

SUMMARY

The possibility of injury from diagnostic x-rays in the practice of Urology is discussed.

The principal factors responsible for excessive radiation exposure are given.

Simple, effective means to reduce radiation hazards are outlined.

Routine use of film badges to indicate actual radiation exposure is recommended.

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[10] Tochilin, E., Davis, R. H. and Clifford, J. A.: Calibrated Roentgen-ray film badge dosimeter. Am. J. Roent. & Rad. Ther., **64**: 475–488, 1950.

PROGRAM, ANNUAL MEETING OF NORTHEASTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION, QUEBEC CITY, CANADA, SEPTEMBER 20–22, 1954

SEPTEMBER 20

A CASE OF TETANY IN UREMIA, RESPONDING TO THERAPY, Albert G. Rowe, Hornell, N. Y.
DISCUSSION. To be opened by William E. Ortved, Toronto, Canada

PORPHYRIA: A MEDICAL CONDITION PRESENTING A SURGICAL PROBLEM, N. E. Berry, Kingston, Ontario, Canada
DISCUSSION.

EXPERIENCE WITH COMPLICATIONS FOLLOWING UROLOGIC SURGERY, W. J. McMartin, President A.U.A. (by invitation), Omaha, Nebr.
DISCUSSION.

SURGICAL TREATMENT OF HORSESHOE KIDNEYS: COMPARISON OF RESULTS AFTER VARIOUS TYPES OF OPERATIONS, O. S. Culp (by invitation), Mayo Clinic, Rochester, Minn.
DISCUSSION.

PROSTATECTOMY, THEN AND NOW, F. J. Parmenter, Buffalo, N. Y.
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MOVIE: THE USE OF X-RAY MOTION PICTURE TO STUDY BLADDER AND URETHRAL FUNCTION IN MAN AND DOG, John A. Benjamin, Rochester, N. Y.
DISCUSSION. John A. Benjamin, Rochester, N. Y.

REFLECTIONS ON SOME PROBLEMS RELATING TO URETERO SIGMOID ANASTOMOSIS, Reed M. Nesbit (by invitation), Ann Arbor, Mich.
DISCUSSION.

EXPERIENCES IN THE TREATMENT OF CARCINOMA OF THE BLADDER WITH RADIOACTIVE ISOTOPE OF GOLD, J. L. Hamilton, Pittsburgh, Pa.
DISCUSSION. Conrad A. F. Kuehn, Pittsburgh, Pa.

HYDATID CYST OF KIDNEY, R. Grant Reid, Montreal, Canada.
DISCUSSION. To be opened by H. L. Schlesinger, Plattsburg, N. Y.

PRESIDENTIAL ADDRESS, Dr. Albert M. Crance, Geneva, N. Y.

SEPTEMBER 22

CLINICAL STATISTICAL SURVEY OF RENAL TUMORS ENCOUNTERED IN OUR PRACTICE, Patrick S. Mullins, Utica, N. Y.
DISCUSSION. To be opened by David W. Kline, Greenville, Pa.

TUMORS OF THE URINARY BLADDER: A CLINICO-PATHOLOGICAL ANALYSIS OF OVER 2000 SPECIMENS AND BIOPSIES, M. M. Melicow (by invitation), New York, N. Y.
DISCUSSION.

MANAGEMENT OF URETHRAL CARCINOMA IN THE FEMALE, William J. Staubitz, Lawrence M. Carden, Oscar J. Oberkircher and Melbourne H. Lent, Buffalo, N. Y.
DISCUSSION. To be opened by M. M. Melicow, New York, N. Y.

LESIONS OF THE KIDNEY IN ACUTE RENAL FAILURE, Douglas Waugh (by invitation), Montreal, Canada
DISCUSSION.

WILMS'S TUMOR, A. B. Hawthorne, Montreal, Canada.
DISCUSSION. To be opened by Douglas Waugh, Montreal, Canada.

VESICAL NECK OBSTRUCTION IN THE FEMALE, Ernest F. Hock, Binghamton, N. Y.

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SECTION MEETINGS

Northeastern Section—Chateau Frontenac, Quebec City, Quebec, September 19–22, 1954
North Central Section—Detroit, Mich., October 7–9, 1954
South Central Section—Colorado Springs, Colo., October 18–20, 1954
Western Section—Hotel del Coronado, Coronado, Calif., January 24–27, 1955
Southeastern Section—Hotel Jung, New Orleans, La., March 21–23, 1955
Mid-Atlantic Section—Haddon Hall, Atlantic City, April 13–16, 1955

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ADRENAL INSUFFICIENCY AS RELATED TO SURGICAL SHOCK

ROBERT S. HOTCHKISS AND SYDNEY GORDON

From the Department of Urology, New York University Post Graduate Medical Schools and Department of Urology (Fourth Division) Bellevue Hospital, New York, N. Y.

The hazards of surgery are well appreciated in relation to patients having known adrenal insufficiency, such as Addison's disease.[1] Certain effective precautions are taken to prepare for and combat the shock and electrolytic imbalance that are to be anticipated. Acute adrenal cortical insufficiency, moreover, may also occur as a serious postoperative complication in patients not previously known to have adrenal disease. Such a distressed patient may fail to survive if the hypo-adrenalism remains unconsidered and unrecognized, for the essential therapy will not be supplied. For reasons to be given, we believe the urologist should be particularly alert to the possibility of acute adrenal insufficiency developing incident to the stress of an operation.

The clues for the diagnosis and the rationale of treatment of hypo-adrenalism are based upon the principles of adrenal physiology. It would therefore be appropriate to review the hypothalamus pituitary adrenal cortical axis for this neuro-endocrine complex is concerned with stress and the physiologic reactions thereto.

PHYSIOLOGY

The hypothalamus receives and responds to the stimuli of stress thereby releasing the corticotrophin hormone (ACTH). See figure 1. ACTH, in turn, is responsible for the elaboration of three groups of steroid hormones in the cortex of the adrenal glands. The stress phenomenon concerns principally the mineral corticoid group, of which desoxycorticosterone is an important member, for salt and water metabolism is profoundly affected by this group. A second group of adrenal hormones, designated as the glucocorticoids, are concerned primarily with the metabolism of fat and the conversion of protein to carbohydrates. In their absence the organism must rely completely on carbohydrate stores with a consequent depletion of the glycogen content of the liver. A third group of adrenal hormones is known as the androgenic steroids, but their functions are not particularly germane to the topic under discussion.

The effects of adrenalectomy in the experimental animal are well known. Comparable physiologic alterations develop in the postoperative patient if there is an inadequate release of corticoids in response to the stress of surgery. The primary changes noted in acute adrenal insufficiency precipitated by surgical stress are: a) an immediate, rapid, loss of sodium and chloride from the blood serum with concomitant increase in their concentration in the urine; and b) a marked decrease in the vascular space with consequent hypotension and a decreasing urinary output terminating in anuria.

Accepted for publication February 18, 1954.

[1] Thorn, G. W.: Diagnosis and Treatment of Adrenal Insufficiency. Springfield, Ill.: Charles C. Thomas, Publisher.

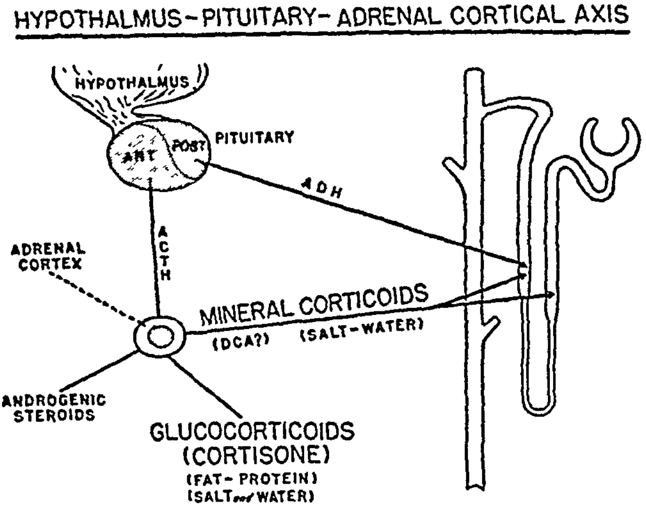

FIG. 1

The equilibrium between serum sodium, intracellular sodium, and the urinary excretion of sodium is partly dependent upon the mineral corticoids and the antidiuretic hormone of the pituitary. The antidiuretic hormone remains unopposed if the mineral corticoids are not provided thereby producing an oliguria. Water shifts from the vascular space into the interstitial and cellular compartments of the body.[2-4] See figure 2. Hypotension ensues and contributes to the reduced production of urine by diminished renal blood flow. These violent physiologic disturbances are augmented by loss of serum sodium due to increased excretion into the urine. The serum potassium and serum urea nitrogen increase, presumably because of reduced renal clearance.

The degree of shock is dependent, in the norm, upon the magnitude of the stress. The compensatory output of corticoids during the recovery phase is regulated by the requirements necessary to restore the body equilibrium. If these hormones are not available in sufficient amounts, such as in adrenal insufficiency, DCA may be administered as a substitute. Salt is then retained, water shifts back from the cells to the vascular space, the blood volume is restored, the blood pressure rises and diuresis is precipitated, for the adrenal hormones now oppose the pituitary antidiuretic hormone. With resumption of renal function there is increased clearance of potassium and urea, allowing a return to normal blood levels. The glucocorticoids (cortisone) have a relative minor effect upon the regulation of salt and water as compared to the mineral corticoids (DCA). Nevertheless, if cortisone is given in excessive amounts over a period of time, salt and water will be retained in the body.

It is quite apparent that a valuable purpose would be served if some simple test could be applied to appraise the reliability of the adrenals to produce sufficient corticoids to defend the body adequately against the stress of a contemplated surgical procedure. It must be borne in mind that failure to respond

[2] Loeb, R. F.: Bull. N. Y. Academy of Med., 18: 263-270, 1942.
[3] Harrop, G. A.: Bull. Johns Hop. Hosp. 59: 11-23, 1936.
[4] Smith, Homer: The Kidney. New York: Oxford University Press, 1951.

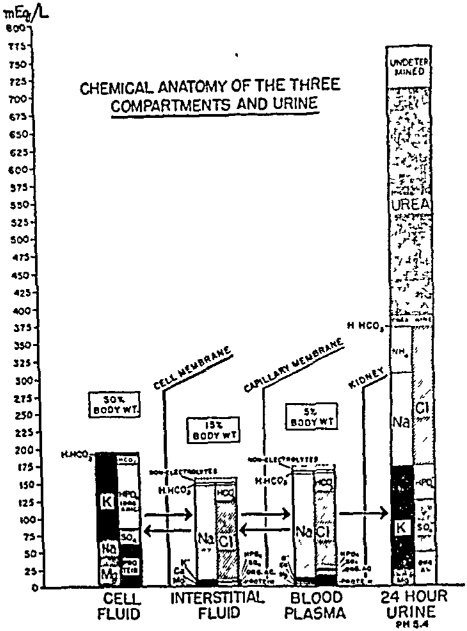

FIG. 2

may occur at any of the three levels of the hypothalmus-pituitary-adrenal axis. There are no chemical tests to evaluate the hypothalmic area. At present there is no specific differentiating test for pituitary insufficiency. Formerly, a test for pituitary function was used based upon the premise that epinephrine acted upon the hypothalmus thereby stimulating the pituitary to release corticotrophin. The adrenals, in turn, were then activated causing a fall in the circulating eosinophiles from the previously determined control levels. Pituitary insufficiency was inferred if this drop in eosinophiles failed to develop but was obtained by exogenously administered ACTH. Recent studies in bilaterally adrenalectomized man have shown, however, that epinephrine is capable of producing eosinopenia in the absence of adrenal cortical tissue, thus invalidating the test.

A number of tests have been advocated to determine the capacity of the adrenal cortex to respond to corticotrophin. These have included determination of the 17-ketosteroids and the neutral reducing lipids (11-oxysteroids). The measurement of the 17-ketosteroids urinary output includes the androgenic precursors from both the adrenals and testes and therefore is not an indicator for the adrenal alone. On the other hand, the 11-oxysteroids reflect the production of the glucocorticoids which arise only from the adrenals and probably indicate the total corticoid potentials of the adrenals. Adrenal cortical insufficiency may be detected by a clinical test utilizing these principles. Following the intravenous administration of twenty U.S.P. units of ACTH there is an increase in the 17-ketosteroid urinary excretion of ten to fifteen milligrams (10–15 mg.) above the control level. This is accompanied by a fall of at least eighty-five per cent of the circulating eosinophiles from control levels. Failure to secure these responses indicates primary adrenal cortical insufficiency.[5, 6]

Two other clinical tests of proven value have been employed to diagnose hypo-adrenalism. The Robinson-Kepler-Power water test employs the principle that an individual with hypo-adrenalism excretes less urine following the ingestion of a large quantity of water than does a normal. An intake of 1500 cc water over a 40 minute period will normally result in the excretion of 1200 cc urine during the ensuing 5 hours. A person with Addison's disease is unable to develop diuresis because of unopposed action to the antidiuretic hormone and accordingly will excrete less than 800 cc within that time. The "Salt Deprivation Test" operates upon the fact that an individual with Addison's disease continues to lose salt via the kidney even though he is deprived of dietary sodium. The normal person promptly reduces the amount of excreted salt to conserve his endogenous supply. Within two to six days a crisis will develop in hypo-adrenalism due to salt deficiency, whereas the absence of such a response in a suspected patient makes the diagnosis of Addison's disease untenable.[7]

The foregoing tests are designed to diagnose adrenal insufficiency before an actual crisis develops. Often, however, the surgeon is confronted with unexplained postoperative shock which does not respond to the usual methods of treatment and one may well suspect that the stress of the operation has precipitated adrenal cortical failure. The diagnosis may be supported by four findings: 1) marked hypotension, 2) low blood serum sodium, 3) low blood serum chloride and 4) low carbon dioxide combining power. The serum sodium and chloride determinations are valuable indicators of adrenal function but the diagnosis of hypo-adrenalism cannot be rejected if normal levels are encountered. The hemoconcentration accompanying the adrenal crisis may mask the actual loss of total serum electrolytes by virtue to higher concentration per unit of blood serum. Furthermore normal levels of these electrolytes may prevail in the presence of adrenal insufficiency unaggravated by the stress of surgery, so that serum sodium and chloride determinations prior to surgery are not effective "screening" procedures.

How then is it possible to prepare for a crisis or diagnose adrenal insufficiency if suspected as a postoperative catastrophe? One or more of the foregoing clinical tests may be employed prior to surgery and appropriate prophylactic treatment begun, if indicated. If unexplained shock develops following surgery which is refractory to usual supportive therapy, substitution adrenal therapy may be a life saving measure. Low blood serum sodium chloride and base are valuable aids to support such an assumption.

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[5] Thorn, G. W.: J. Clin. Endocrinol., **13**: 614–616, 1953.

[6] Thorn, G. W.: J. Clin. Endocrinol., **13**: 604–613, 1953.

[7] Soffer, L. J.: Bull. N. Y. Acad. Med., **29**: 101–103, 1953.

It is of advantage to know what type of patient may develop a crisis after an operation. Such might be encountered in one of the following groups.

1) Patients subjected to an extensive surgical procedure.
2) Senile patients with chronic debilitating disease.
3) Psychotic patients.
4) Patients who have urologic disorders.
5) Patients who have been treated with cortisone, hydrocortisone, and/or corticotrophin.

1) *Extensive surgical procedures.* Zimmerman made observations on two groups of patients and recorded results which he attributed to be due to differences in cortical responses to stress.[8] Operations which ordinarily do not produce shock were compared with extensive procedures. Patients who had drastic surgery demonstrated a prolonged fall in serum sodium and chlorides, whereas the changes were less marked when the operation was not severe. He concluded that unusually severe operative stress may exhaust the adrenals, producing a period of relative adrenal insufficiency.

2) *Senile patients with chronic debilitating disease.* With advancing age the 17-ketosteroid output decreases. Bonner has shown that a decreased uric acid response to corticotrophin is to be expected in aged and debilitated patients.[9] Selye has referred to patients in the advanced age group as having poor adaptation to chronic stress. The conclusion drawn from these studies is that this group of patients has subclinical adrenal insufficiency.[10-12]

3) *Psychotic patients.* The psychotic patient has been extensively studied in terms of adrenal activity. Pincus and Hoaglund reported 72 per cent hyporesponsitivity in schizophrenia, using the indices previously mentioned.[13-17] The deficiency was thought to be localized to the adrenal cortex and was not of pituitary origin. Grunebaum confirmed their work utilizing studies on the salt content of sweat.[18] The high perspiratory sodium indicates a deficiency of the adrenals in the regulation of salt in psychotic patients.

4) *Patients who have urological disorders.* Special situations confront the urologist in surgical care in addition to the common problem of age and debilitation. Patients who have had previous renal surgery may have suffered unrecognized but irreparable damage to the corresponding adrenal incident to manipulation of the kidney. The accidental removal of an adrenal is possible during difficult nephrectomy. If surgery becomes necessary on the remaining or unoperated kidney the solitary adrenal might also be traumatized so that its function is impaired during the immediate postoperative period. Furthermore,

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[8] Zimmerman, B.: Surgical Forum. Philadelphia: W. S. Saunders Co., 1951.

[9] Bonner, C. D.: Geriatrics, 5: 203-207, 1950.

[10] Kowalewski, K.: J. Gerontology, 5: 222-225, 1950.

[11] Goldsieher, J. W.: Gerontology, 7: 47-53, 1952.

[12] Timiras, P.: Geriatrics, 4: 225-229, 1949.

[13] Pincus, G.: Am. J. Psych., 106: 651-659, 1950.

[14] [illegible], 1946.

[illegible] 1949.

[illegible] 1946.

[illegible]-88, 1949.

[illegible] eurol. & Psych., 63: 444-452, 1950.

unilateral congenital absence of the adrenal presents an uncommon but definite hazard during kidney operations. Metastatic carcinoma of the prostate has been known to replace both adrenals and extensive involvement of the adrenals by tuberculosis is always a possibility when the tuberculosis of the genito-urinary organs requires surgery. Atrophy of the contralateral adrenal in instances of adrenal tumor is so well known that further comment is unnecessary. Two common practices deserve attention in relation to urologic patients. The custom of forcing fluids after operation may constitute a most effective Robinson-Kepler-Power water test in the aged patient with hyporesponsive adrenals. Significant water retention due to the unopposed action of the antidiuretic hormone may result. Secondly, the urologist often withholds parenteral saline during the first few postoperative days, for good reason, with patients having cardiac disease. Salt deprivation coupled with adrenal exhaustion may produce a crisis as described in the salt deprivation test for Addison's disease.

5) *Patients who have been treated with cortisone, hydrocortisone and/or corticotrophin.* There is considerable evidence to support the view that the therapeutic administration of adrenal cortical hormones may suppress adrenal function and induce atrophy. Corticotrophin and cortisone also may produce histologic alterations in the pituitary gland impairing the production of endogenous corticotrophin. These atrophic changes may lead to acute adrenal cortical insufficiency in the face of sufficient stress, such as an operation. Salassa and associates conclude that "any patient who has received sufficient cortisone within three to six months should receive prophylactic therapy," before an operation.[19] Adrenal suppression may occur with a minimal dosage after only 5 days of treatment and render the individual susceptible to a crisis long after the treatment has been discontinued. Consequently, all patients who have had prior treatment with these hormones should, at least, be observed with greatest care and treated promptly if signs of hypo-adrenalism develop following an operation.

ILLUSTRATIVE CASES

The following case studies are presented as examples of proven adrenal insufficiency or, as illustrations of severe shock following stress apparently relieved by substitution therapy.

Case 1. Admission No. 10140 (1947) Bellevue Hospital. A 72 year old man was admitted to the Department of Urology, Bellevue Hospital in 1947 with a diagnosis of recurrent bladder tumor. He had had numerous admissions for transurethral fulguration of this lesion, but had consistently refused more extensive surgery. His blood pressure on admission was 150/90. The physical examination was essentially negative. Cystoscopy on this admission revealed a sessile neoplastic lesion. A cystotomy was done and the tumor was fulgurated by electrocautery. During the operation unexplained shock developed and the patient's blood pressure fell to 80/50. He failed to respond to the usual therapy for surgical shock and expired within thirty hours after operation without having regained consciousness. His blood pressure remained at shock levels until his death.

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[19] Salassa, R. M.: J.A.M.A., 152: 1509–1515, 1953.

Autopsy revealed complete replacement of both adrenals by metastatic tumor. The para-aortic glands were similarly involved.

Comment: This proven case of adrenal insufficiency was completely unsuspected prior to operation. Adequate treatment to reverse the insufficiency was unavailable at that time.

Case 2. Admission No. 82113 (1951) Bellevue Hospital. W. L., a 66 year old white man, was admitted to the Neuropsychiatric Division of Bellevue Hospital in 1951, with a long history of prostatism. System review and physical examination revealed an apparently healthy adult male, appearing younger than his stated age. His blood pressure was 170/80 and his prostate was two times enlarged and of benign consistency. An excretory urogram revealed a large vesical calculus, a hydronephrotic right kidney, and a nonfunctioning left kidney.

A suprapubic cystolithotomy was done with almost no loss of blood. The patient experienced no difficulty until 48 hours after operation, when unaccounted for profound shock suddenly developed. His blood pressure was recorded as 70/0. Routine therapy for shock was instituted, and during the next 24 hours he received oxygen, 750 cc plasma and 1,000 cc of whole blood in addition to parenteral fluids. His general condition remained unchanged and he became anuric. Blood serum revealed a chloride of 80 mEq/L (normal 104) and serum sodium of 114 mEq/L (normal 140–145).

Adrenal hormonal therapy was given together with parenteral sodium chloride therapy. His blood pressure quickly rose to preoperative levels, diuresis promptly began, and he recovered from the state of shock. His electrolytes reverted to normal within the next five days with the exception of an elevated blood serum nonprotein nitrogen which was attributed to his pre-existing renal disease.

A transurethral resection of the prostate was recommended but the patient refused consent to this procedure. When examined at subsequent visits to the hospital following his discharge, he was without evidence of clinical hypoadrenalism. The 24 hour 17-ketosteroid output one month after recovery was 1.5 mg.

Case 3. Admission No. 2752 (1952) Bellevue Hospital. M. B., an 84 year old white man, was admitted to the Neuropsychiatric Division of Bellevue Hospital. He had been transferred from another hospital where he had become unmanageable. A history suggestive of prostatic obstruction of many years' duration was obtained from relatives. He was found to have an enlarged heart, hepatomegaly, and benign prostatic hypertrophy producing residual urine to the amount of 250 cc. His blood pressure was 230/100. Restraints were constantly required to prevent him from removing his catheter. Despite sedation, he was under constant emotional and physical stress protesting and struggling to free himself from his restraints. At the end of 24 hours the patient's blood pressure rapidly fell to imperceptible levels. His skin was cold and clammy and the 24 hour output of urine decreased to 200 cc despite an adequate intake of fluids.

Blood samples were secured at this time and analyses revealed the following: Sodium, 116 mEq/L; chloride, 70 mEq/L; carbon dioxide combining power, 30 volumes per cent.

Adrenal cortical hormones and parenteral sodium chloride were given. Within 48 hours, the patient's blood pressure was restored to the former hypertensive levels and his serum electrolytes returned to normal. A twenty-four hour 17-ketosteroid output was 1.3 mg.

A suprapubic cystotomy was done on the fourteenth day after admission. The patient experienced no difficulty for the first 48 hours but thereupon sudden profound shock developed. Adrenal substitution therapy and parenteral saline were again resumed. Serum electrolytes before therapy revealed the following: Sodium, 106 mEq/L; chlorides, 78 mEq/L; and carbon dioxide combining power 42 volumes per cent. The signs of shock were promptly controlled, his blood pressure was restored, and within 48 hours his serum electrolytes were normal. Three weeks later, prophylactic adrenal substitution therapy was given and a suprapubic prostatectomy was performed without signs of shock, or with any clinical or laboratory evidence of adrenal insufficiency. However, on the fourth postoperative day, broncho-pneumonia developed which failed to respond to therapy. The patient died on the eighth postoperative day. No autopsy was obtained.

Case 4. Admission No. 14746 (1952) Bellevue Hospital. L. G., an 84 year old man, psychotic, and blind secondary to glaucoma, had known arteriosclerotic heart disease with previous episodes of failure, and suffered from Parkinson's disease. There was a 6 year history of prostatism and he was admitted to Bellevue Hospital in acute urinary retention. His prostate was enlarged and nodular. The blood serum phosphatases were normal and there was no roentgen evidence of skeletal metastases.

After 8 days of catheter drainage, a transurethral prostatectomy was done. During the operation the blood pressure suddenly fell to imperceptible levels and was restored and maintained at 70/0 only by continuous intravenous neosynephrine. Adrenal cortical hormones and parenteral saline were given and within one hour the neosynephrine was discontinued. Samples of blood taken at this time revealed sodium, 113 mEq/L; potassium, 3.8 mEq/L; chloride, 82 mEq/L. His blood pressure rose promptly to 130/70 as compared to 170/84 prior to operation. Blood serum electrolytes 24 hours later were sodium, 130 mEq/L; potassium, 2.7 mEq/L; chloride, 138 mEq/L.

During the following week signs of cardiac failure gradually developed as evidenced by pulmonary and peripheral edema. Despite fluid restriction, elimination of sodium and chloride, the use of diuretics and potassium, he died 8 days following surgery. His death was primarily attributed to heart failure.

Comments. Cases 2 and 3 were elderly psychotic, chronically ill men with multiple system diseases. Each experienced severe shock after a surgical procedure although such could not be explained by blood loss or untoward events in the conduct of the surgery. The conventional methods for combating shock were not rewarding but treatment designed to provide corticoids and correct electrolyte imbalance appeared effective in overcoming the immediate crisis.

Case 4 illustrates the multiplicity of problems inherent in attempting to maintain electrolyte and water balance in the presence of congestive heart failure complicated by probable adrenal insufficiency. Sodium and chloride blood serum levels were excessive on the second postoperative day. As a result we have since discontinued the use of 5 per cent sodium chloride infusions and now employ only isotonic sodium chloride. There have been no other instances of higher than normal levels of sodium and chlorides since salt has been used more sparingly.

Case 5. Admission No. 8978 (1953) Bellevue Hospital. H. S., a 68 year old man, was admitted to the Fourth Surgical Division (Urology) of Bellevue Hospital with a history of gross hematuria on three occasions during the year prior to admission. Two years previously, stones had been removed from each kidney.

The patient's blood pressure on admission was 170/100. The physical examination was essentially negative except for bilateral loin scars. Urologic investigation revealed numerous calculi in a hydronephrotic left kidney. There were several small right renal calculi. Nonprotein nitrogen was 50 mg. per cent.

A left nephrolithotomy was done with moderately severe blood loss which was replaced immediately. Following the operation, the patient's blood pressure remained quite labile despite further blood transfusions. Twenty-four hours after operation the blood pressure dropped to 70/30 and the patient lapsed into severe shock. Adrenal cortical hormones and parenteral sodium chloride were given, after appropriate electrolyte studies had been done. Without further transfusions the patient's blood pressure rose to 150/70 within two hours, and remained stable at that level. His urinary output, which had been 300 cc in the previous 24 hours, increased to 1600 cc in the second 24 hour period. The patient was maintained on adrenal cortical hormones for one week and made an uneventful recovery. Serum electrolyte studies prior to the initiation of hormonal therapy were not remarkable, as revealed by the following: Sodium, 123 mEq/L; potassium, 4.5 mEq/L; chloride, 92 mEq/L.

Comment. The prompt response to this regimen strongly suggests that adrenal cortical insufficiency accounted for shock, hypotension, oliguria, and collapse.

Case 6. Admission No. K57190 (1952) University Hospital. A 52 year old woman was admitted to University Hospital with a diagnosis of recurrent staghorn calculus in a solitary kidney. The contralateral kidney had been removed some years previously for calculous pyonephrosis. The right kidney had been operated upon by one of us (R. S. H.) 18 months previously, at which time a nephrolithotomy and a ureterotomy for stricture were performed.

The kidney was again freed, the pedicle clamped with rubber shod clamps, and a kidney split performed to remove a large staghorn calculus. At no time during the procedure was there excessive bleeding and the apparent blood loss was replaced during operation. One hour after completion of the surgery the patient's blood pressure fell to 50/20 accompanied by profound shock. There was no evidence of unusual postoperative bleeding. Adrenal cortical hormones and parenteral saline with neosynephrine were given by the intravenous route. The clinical response was immediately satisfactory and within 12 hours the neosynephrine was discontinued. On the third postoperative day an electrolyte survey revealed normal serum sodium chloride, carbon dioxide combining power, and nonprotein nitrogen. An uneventful convalescence followed.

Case 7. Admission No. K51292 (1952) Bellevue Hospital. J. S., a 64 year old man, who had had a prostatectomy one month previously in another hospital was admitted to the Fourth Surgical Division (Urology), Bellevue Hospital. On his first postoperative visit to his urologist, urethral dilatation was done and he fainted. Following his recovery he returned home and once again collapsed. When admitted to Bellevue Hospital, 2 hours later, he was in profound shock. His blood pressure was unobtainable and his pulse weak. There was no evidence of a rupture of the bladder or of the urethra. The patient remained stuporous, hypotensive, and oliguric for the next 24 hours despite vigorous antishock treatment. He was then given adrenal cortical hormones and parenteral saline. Within four hours his blood pressure had risen to 110/60 and his skin was dry and warm. A diuresis followed and he made an uneventful recovery. Subsequent investigations, including electrocardiography, failed to reveal any specific demonstrable cause for his cardiovascular collapse.

Case 8. Admission No. K55951 (1952) University Hospital. Miss M. M., a 23 year old girl and a known schizophrenic, was admitted to University Hospital because of persistent right renal pain and pyuria. Retrograde studies revealed caliectasis in the upper pole of the right kidney. Urinary sediment was searched for tubercle bacilli but none were found. An abscess of the upper pole of the right kidney was discovered and drained when the kidney was exposed. A febrile postoperative course led to the conclusion that a perinephric abscess had developed. Three weeks after the first operation the wound was opened and a large perinephric abscess was discovered. A nephrectomy was done and drains were left in the fossa. Within 6 hours her blood pressure fell to 40/0 and she exhibited all signs of severe shock. It was assumed that the difficulties could be attributed to postoperative hemorrhage at the site of the renal pedicle. Multiple transfusions were given without improvement and within 6 hours she was returned to the operating room. The wound was opened but, as no hemorrhage had occurred, it was closed. Adrenal cortical hormones and parenteral saline were then given, and additional transfusions were withheld. The patient's blood pressure rose to preoperative levels within 2 hours, and at no subsequent time was there cause for concern. Decreasing amounts of cortisone were given for the next 2 weeks and she was discharged without complaints.

Comments: Cases 6, 7 and 8 suffered severe shock following stress. The blood electrolyte studies were not secured to support the assumption that hypoadrenalism was the major factor causing distress, for the sudden onset and extreme severity of symptoms demanded prompt emergency treatment. The response to corticoids, when other methods failed, persuade us to conclude that specific effects had taken place which, indeed, were life saving measures.

PLANS OF TREATMENT

Schedule I. Prophylactic Treatment

Should a diagnosis of adrenal insufficiency be established prior to operation, some form of prophylaxis is indicated. The regimen used on the Fourth Division

Urology, Bellevue Hospital is similar to that employed prior to adrenalectomy for prostatic carcinoma.

Day before surgery.

5 mg. desoxycorticosterone acetate in oil intramuscularly.

Cortisone 50 mg. intramuscularly every 6 hours to a total 200 mg. Blood serum sodium and chloride.

Day of surgery.

5 mg. desoxycorticosterone acetate.

50 mg. cortisone every 4 hours.

Pulse, temperature and blood pressure recorded every 2 hours.

Morphine and related substances used sparingly.

First postoperative day.

3 mg. desoxycorticosterone.

50 mg. cortisone every 6 hours.

Blood serum sodium and chloride.

Second postoperative day.

1 mg. desoxycorticosterone.

50 mg. cortisone every 8 hours and thereafter, gradually reduced as indicated on subsequent days. The patient should receive 1000 cc of 5 per cent glucose in isotonic saline intravenously on the day of operation, plus whatever additional parenteral fluids are considered advisable as determined by the patient's response to operation and his preoperative dietary regimen.

Schedule II. Active Therapy

Active therapy for acute adrenal insufficiency developing in a patient not previously suspected of adrenal cortical insufficiency.

Hormones.

10 mg. desoxycorticosterone acetate in oil intramuscularly every hour for 3 doses.

50 mg. cortisone intramuscularly every 2 hours until the systolic pressure is maintained above 100 mm. of mercury. The subsequent hormonal requirements are judged according to the patient's response. (See Schedule I).

Fluid and electrolytes.

1) One thousand cubic centimeters of 5 per cent glucose in isotonic saline is started at once at the rate of 60–80 drops per minute. A second infusion of 1000 cc of glucose-saline is then given slowly at the rate of 20 to 30 drops per minute.

2) Concomitant with above fluids, a solution of 1000 cc of 5 per cent glucose in water is given through a second vein. To this solution is added 6 cc of 1 per cent neosynephrine or 4 mg. of norepinephrine. The rate that this solution is administered is determined by the patient's blood pressure response. The systolic blood pressure should be kept above one hundred by the neosynephrine solution, and the rate of flow gradually reduced as the blood pressure rises in response to the administration of saline and the

adrenal corticoids. In most cases, it will be possible to discontinue the neosynephrine solution within four hours after the initiation of salt and hormonal therapy. The subsequent electrolyte and fluid needs of the patient are determined by the clinical reaction, blood pressure, urinary output and serum electrolyte concentrations in accordance with plan outlined in Schedule 1.

Schedule III. An Alternate Schedule of Hormonal Therapy of Acute Adrenal Insufficiency

Ten cubic centimeters of lipo-adrenal cortical extract may be administered intramuscularly every hour for 3 doses. This is recommended by Dr. Herbert Kupperman as having greater latitude in dosage with less danger of precipitating pulmonary edema than if DCA is used.

Fifty cubic centimeters of aqueous cortical extract may be added to the isotonic saline infusion. If this material is not available intravenous solutions of cortisone or hydrocortisone may be used. The intravenous solutions are utilized more rapidly than intramuscular cortisone, thereby producing effects more promptly.

CONCLUSIONS

Acute adrenal insufficiency is a surgical hazard capable of causing death.

Surgical stress may precipitate acute adrenal insufficiency in patients previously unsuspected of having adrenal cortical inadequacy.

Effective preoperative and postoperative treatment may protect the patient from the crisis of hypo-adrenalism.

Tests for adrenal cortical function are available but it is not safe to assume that normal responses to such tests insure adequate cortical function necessary to cope with the stress of an operation.

There are no definite means to identify patients having adequate adrenal activity for uncomplicated life but which are incapable of providing sufficient corticoids to defend the body against severe stress.

In the event that unexplained shock develops following surgery which does not respond to the usual treatment, and a reasonable doubt arises that hypo-adrenalism exists, it is best to use appropriate therapy rather than withhold treatment. There is little reason to fear that such measures will be injurious even though they have been unnecessary in some instances.

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THE DIAGNOSIS OF HYDRONEPHROSIS BY PERCUTANEOUS RENAL PUNCTURE

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The radiologic diagnosis of hydronephrosis is usually adequately established by excretory or retrograde urography. There are, however, occasional cases in which for various reasons conventional radiographic procedures fail to yield satisfactory information.

It is the purpose of this paper to show that under these circumstances the diagnosis of hydronephrosis may be ascertained by direct renal puncture with injection of contrast medium into the dilated kidney pelvis or calyces. Our studies were stimulated by various reports describing the method of renal aspiration biopsy[1, 2] as well as by the work of Lindblom[3, 4] who advocated percutaneous renal puncture and injection of radiopaque media for the differential diagnosis of renal tumors and cysts.

The method of renal puncture will be briefly described and illustrative cases of hydronephrosis will be reported in which this procedure was utilized to advantage.

METHOD

Local anesthesia is usually employed although a general anesthetic might be given to young, apprehensive, or unco-operative patients. Suitable doses of barbiturates are administered one to two hours preceding the procedure to minimize procaine reactions. The patient is placed prone on a full length x-ray table and the entire middorsal region cleansed and prepared. An area just beneath the last rib on the suspected side and just lateral to the longitudinal muscles of the back is taken as the site for puncture. A skin wheal is raised with 1 per cent procaine solution and the abdominal wall infiltrated. In selected cases supplementary blockage of the lower intercostal nerves may be done. A 5 or 10 cc glass piston syringe attached to a 5 inch 18 gauge needle is used. If a mass is palpable the needle is directed towards the mass. Otherwise radiographic localization of the renal area should be performed with the patient in the prone position. Lead numbers on the patient's skin may serve as proper external landmarks.

When urine is obtained a small amount is aspirated for examination and contrast medium (20–30 cc of 35 per cent diodrast in this series) is immediately

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[1] Dean, A. L.: Treatment of solitary cyst of kidney by aspiration. Trans. Am. Assoc. Genito-Urin. Surg., **32**: 91–95, 1939.

[2] Iverson, P. and Brun, C.: Aspiration biopsy of kidney. Am. J. Med., **11**: 324–330, 1951.

[3] Lindblom, K.: Percutaneous puncture of renal cysts and tumors. Acta Radiol., **27**: 66–72, 1946.

[4] Lindblom, K.: Diagnostic kidney puncture in cysts and tumors. Am. J. Roentgenol. & Rad. Therapy, **68**: 209–215, 1952.

A markedly enlarged left kidney pelvis with very small calyces was detected (fig. 2). None of the contrast medium was seen to pass into the ureter or bladder.

On subsequent operation a large hydronephrosis due to ureteropelvic obstruction by a stricture with almost complete parenchymal destruction was discovered. A nephrectomy was performed. The convalescence was uneventful.

Comment: This 8 year old boy presented himself with a large mass in the left side of the abdomen. On cystoscopic examination the left ureteral orifice could not be detected. In order to avoid another cystoscopic instrumentation and general anesthesia it was considered less noxious to the patient to perform renal puncture. A large hydronephrotic kidney was demonstrated without difficulty and the patient withstood the procedure exceedingly well.

Case 3. T. E., a 42 year old Negro, was admitted to Grady Memorial Hospital in February 1953, with a diagnosis of urethral fistulas. Following a gonorrheal infection in 1934, a urethral stricture developed which required repeated instrumentations and several hospital admissions. In 1948 he suffered from a peri-urethral abscess which necessitated drainage.

Since that time multiple urethral fistulas had developed which extended into the perineum and persisted up to the present hospital admission.

On physical examination a large pelvic mass was detected which on barium enema was seen to elongate the rectum displacing it toward the right side. No intrinsic lesion of the rectum was recognized.

The laboratory findings indicated slight albuminuria. The urinalysis disclosed 14 to 16 red blood cells and 5 to 7 white blood cells per high power field. The other laboratory findings were not remarkable.

Excretory urography demonstrated right hydronephrosis and hydro-ureter. On immediate and delayed roentgenograms no excretion of contrast medium on the left side was detected.

In order to visualize the left upper urinary tract, a left renal puncture was performed and 30 cc of grossly purulent urine were obtained. Injection of 25 cc of 35 per cent diodrast made it possible to outline the left upper urinary tract. The kidney pelvis and several major calyces were found to be markedly distended. The entire ureter was tortuous and dilated. On upright tilting the contrast medium passed downward through the ureter to the level of the upper sacrum where a complete obstruction was encountered (fig. 3). None of the contrast medium passed into the urinary bladder. Several days later a left nephrostomy was performed which is still functioning at the present time.

Subsequently an advanced carcinoma of the urinary bladder was demonstrated, which apparently had caused obstruction of the left ureter.

Comment: In this patient multiple urethral fistulas and strictures did not permit retrograde pyelographic examination. Since, on excretory urography, the left upper urinary tract could not be outlined, renal puncture gave adequate information as to the appearance of the left ureter and kidney pelvis.

Case 4. R. M., a 47 year old Negro, was admitted to Grady Memorial Hospital in September 1952 because of epigastric pain, vomiting, weakness, poly-

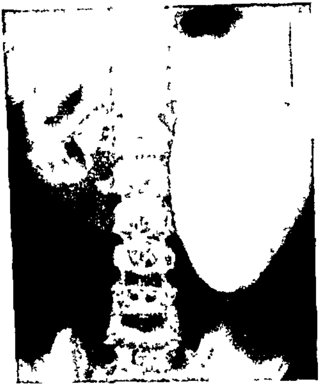

FIG. 2

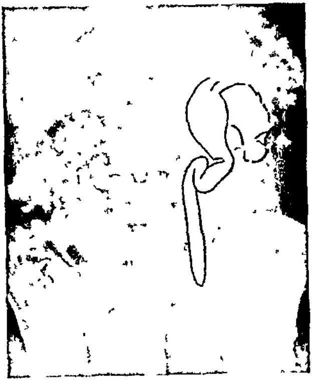

FIG. 3

FIG. 2 Case 2 Huge hydronephrosis shown by renal puncture and injection of contrast medium.

FIG. 3. Case 3. Retouched. Marked dilatation of left upper urinary tract and ureteral obstruction demonstrated by renal puncture. Residual barium in colon shows large pararectal mass.

uria, and nocturia. His blood pressure was markedly elevated and there was evidence of moderate anemia. The laboratory findings indicated considerable nitrogen retention and the urinary excretion of phenolsulfonphthalein was not appreciable for a 2 hour period. A tentative diagnosis of chronic glomerulonephritis or chronic pyelonephritis was made and urologic consultation was requested to rule out an obstructive process of the urinary tracts.

Retrograde pyelography disclosed moderate left hydronephrosis probably due to ureteropelvic obstruction. On this examination it was not possible to introduce a catheter into the right ureter, nor could the right urinary tract be visualized by intravenous urography. On the following day under spinal anesthesia, another attempt was made to catheterize the right side but was again unsuccessful. An indwelling catheter was now placed into the left ureter to secure drainage of the left kidney.

Since the patient's clinical condition did not improve and he continued to have elevated temperatures, it appeared desirable to gain information about the right upper urinary tract. The right kidney pelvis was aspirated through the flank and 30 cc of grossly purulent material were obtained. After injection of 25 cc of 35 per cent diodrast, slight dilatation of the kidney pelvis and calyces and tortuosity and dilatation of the upper segment of the ureter became apparent (fig. 4). The opacified right ureter terminated abruptly at the level of the third lumbar vertebra but in follow-up films some of the contrast medium was noted to have passed into the urinary bladder. A right nephrostomy was then performed and on operation the entire ureter was found to be densely bound down by extensive inflammatory changes. The nephrostomy was removed in 8 weeks. In November 1952 a left pyeloplasty was carried out. The

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RENAL CHANGES IN PARAPLEGIA AS SCREENED BY ROUTINE EXCRETORY UROGRAPHY

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Experience has shown that one of the complications of spinal cord lesions is upper urinary tract involvement because of infection, calculosis, vesico-ureteral reflux and obstruction due to ureteral kinking associated with and without reflux.[1, 2, 3, 4, 5, 6] In order to evaluate the visible amount of pathological changes in the upper urinary tract, 315 pyelograms were screened for study at random. The purpose was to discover: 1) the general incidence of pathological changes irrespective of level and 2) to evaluate what part the following factors played in renal disease, a) the level of the spinal cord lesion, b) the completeness or incompleteness of the lesion, c) the time elapsed since the injury, and d) whether the right or left kidneys were affected more often.

Excretory urograms show both the anatomy and function of the kidneys; therefore, a routine was initiated whereby every patient underwent shortly after admission excretory urography and thereafter at yearly or even more frequent intervals. The patients periodically had blood urea nitrogen, nonprotein nitrogen, and phenolsulfonphthalein determinations, and retrograde pyelograms, when indicated, performed. Rogers and Bors[7] have reported their experience with tests of dilution-concentration, nonprotein nitrogen and phenolsulfonphthalein in paraplegia which dealt with the functional aspect of renal changes. It was believed that the excretory urograms supplied the best morphological information necessary for further studies.

In order to answer the questions put forth above, the excretory urograms of 315 patients were reviewed. Two hundred and eighty-nine patients had traumatic cord lesions, 171 of which were complete and 118 incomplete (tables 1 and 2). Twenty-six patients had either disease or tumor of the spinal cord of which 7 were complete and 19 incomplete.

CLASSIFICATION AND METHOD OF STUDY

In order to evaluate the findings, the following classification was used:

Grade 0 or N: Essentially normal pyelogram.

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TABLE 1. *Excretory urogram; statistics*

	COMPLETE LESIONS									INCOMPLETE LESIONS								
	Total Pts	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3	Total Pts	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3
Cervical	7	7	7	0	0	0	0	0	0	33	25	26	6	5	1	0	1	2
Dorsal 1–4	24	19	20	4	2	0	2	1	0	5	4	1	0	0	1	1	0	0
Dorsal 5–8	46	30	35	10	4	2	7	1	0	15	9	13	2	0	2	1	2	1
Dorsal 9–12	77	56	60	8	6	7	3	6	8	17	11	11	4	1	2	1	0	1
D-12, L-1	4	2	2	0	0	0	0	2	2	5	5	5	0	0	0	0	0	0
Lumbar	13	5	7	2	2	6	4	0	0	13	31	33	7	6	2	3	3	1
Grand total	171	119	131	24	14	15	16	13	10	118	85	92	19	15	8	6	6	5
Disease or Tumor	7	3	3	1	2	2	2	1	0	19	11	16	3	2	2	1	0	0

Tabulation presents percentage of normal and pathological kidneys broken down according to various level groups among traumatic spinal cord lesions and also presents results found among nontraumatic cord lesions in group of pyelograms that were graded.

Numerals in vertical columns under heading "total" refer to number of patients' pyelograms graded in each category of neurological levels. All other figures are percentages.

From these percentages figure 1 was created

TABLE 2. *Excretory urogram; percentages*

	COMPLETE LESIONS									INCOMPLETE LESIONS								
	Total Pts.	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3	Total Pts.	R N	L N	R 1	L 1	R 2	L 2	R 3	L 3
Cervical..........	7	100	100	0	0	0	0	0	0	33	75.7	78.7	18.1	15.1	3	0	3	6
Dorsal 1–4........	24	79.1	83.3	16.6	8.3	0	8.3	4.1	0	5	80	80	0	0	20	20	0	0
Dorsal 5–8........	46	65.2	76	21.7	8.6	4.3	15.2	8.6	0	15	60	86.6	13.3	0	13.3	6.6	13.3	6.6
Dorsal 9-12.......	77	72.7	77.9	10.3	7.7	9	3.8	7.7	10.3	17	64.7	64.7	23.5	23.5	11.7	0.8	0	5.8
Dorsal 12, L-1....	4	50	50	0	0	0	0	50	50	5	100	100	0	0	0	0	0	0
Lumbar...........	13	38.4	53.8	15.3	15.3	46.1	30.7	0	0	43	72	76.7	16.2	13.9	4.6	6.9	6.9	2.3
Grand total.....	171	69.5	76.0	14.0	8.1	8.7	9.3	7.6	5.8	118	72	76.2	16.1	12.7	6.7	5.0	5.0	4.2
Disease or tumor.	7	42.8	42.8	14.2	28.5	28.5	28.5	14.2	0	19	76.6	84.2	15.7	10.5	10.5	5.2	0	0

Tabulation presents number of right and left kidneys with their respective grades (normal or pathological). It is broken down according to vertebral level groups or disease or tumor group.

Grade 1: a) Mild blunting of minor calyces, or
b) Mild dilatation of major calyces, or
c) Mild dilatation of renal pelvis, or
d) Combination of the above.
Grade 2: a) Moderate to marked calyceetasis, or
b) Moderate to marked pyelectasis, or
c) Moderate to marked retention of dye, or
d) Combination of above.
Grade 3: a) Gross hydronephrosis.

Although overlapping of grades admittedly occurs, the practical value appears adequate and satisfactory, especially since the evaluation was performed by the author and therefore all films were read similarly.[4]

In order to study the relationships such as time since injury and completeness or incompleteness of the lesion against the various levels of injury, the factors were plotted graphically. Figures 2 and 3 are presented as an example of the largest number of patients in any one respective level.

ANALYSIS

I. General incidence of pathological changes. Six hundred and thirty kidneys were graded. Irrespective of level, completeness of lesion, time since injury and type of spinal cord lesion it was found that: 467 kidneys or 73 per cent were graded as N; 76 or 12 per cent were considered as grade 1; 52 or 8 per cent were grade 2; and 35 or 6 per cent were grade 3. From these figures one then can estimate the number of pathological findings at any given time though there will be some fluctuation.

On examining whether a difference of incidence exists between the traumatic cases and those with disease or tumor irrespective of level, one finds that there is no difference in cases with incomplete lesions, whereas in cases with complete lesions pathological changes are more frequent with the disease or tumor group than with the traumatic group.

II. Incidence of pathological changes.

a) General incidence of pathological kidney changes with regard to vertebral level in traumatic lesions: Figure 1 shows that there is a definite increase in the number of cases with renal disease among patients with a lumbar or D12–L1 level.

This confirms the author's clinical impression that patients classified[1, 2] as having a lower motor neuron type of bladder show more pathological change; the conus medullaris is usually damaged in these cases (D12–L1 and lumbar vertebral levels). Among the causative factors of kidney damage, calculosis and infection are the most common and perhaps also vesico-ureteral reflux, although this is a more frequent event with upper motor neuron lesions.[3]

b) Incidence of pathological kidney changes in relation to the completeness or incompleteness of the spinal cord lesions: Figure 1 reveals that there is no marked difference of incidence in the cervical and dorsal groups, in regard to the completeness of the lesion. However there is a difference in the D12–L1 group and

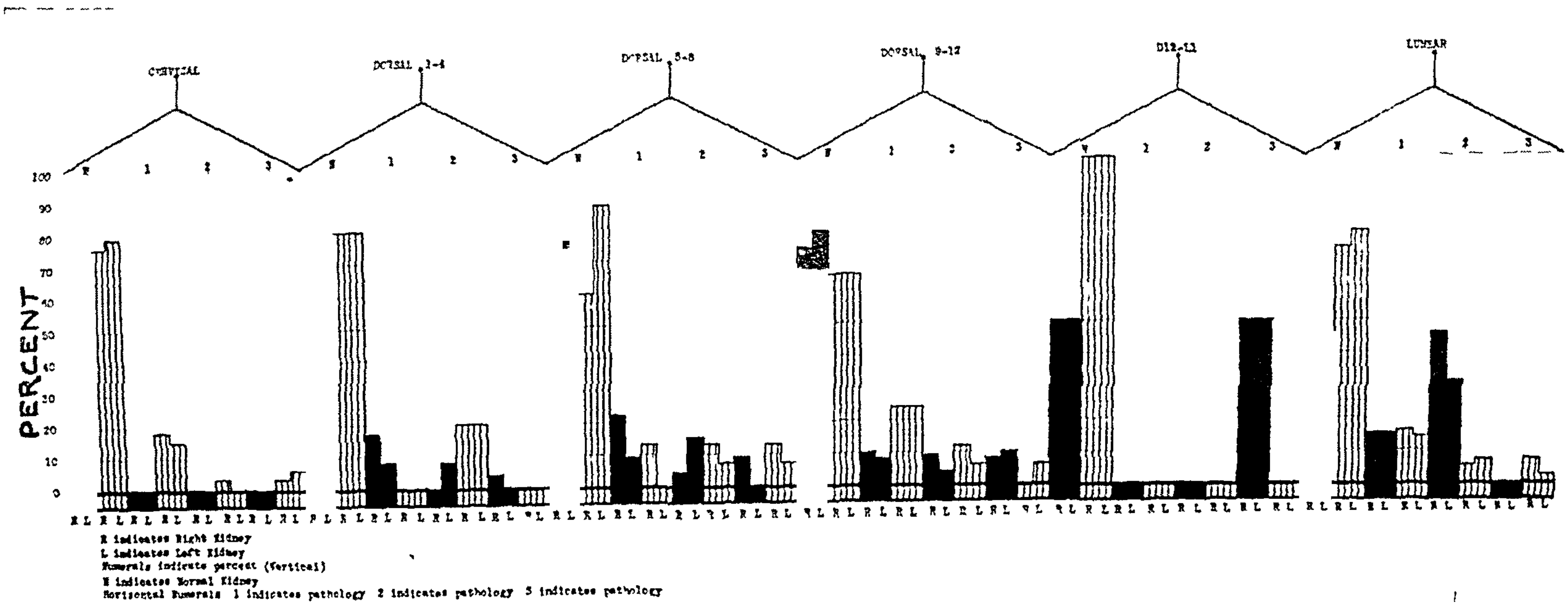

FIG. 1. Depicting percentage (vertical numbers on left) of normal kidneys (N), grade 1 pathological change kidneys (1), grade 2 pathological change kidneys (2), and grade 3 pathological kidneys (3) found in traumatic cord lesions according to vertebral level groups.

Complete (solid dark shaded vertical columns) and incomplete (nonsolid light shaded columns) refer to spinal cord lesion.

Figure graphically shows percentages listed in table 2 (traumatic lesions only).

TABLE 3

Complete lesions

	RIGHT KIDNEY							LEFT KIDNEY						
	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology
Cervical	50							50						
D1–4	55	3	47			28		59	3	46	28	49		
D5–8	68	2	56	45	150	49	97	97	21	59	29	150		
D9–12	74	8	56	23	132	35	174	174	8	54	23	49	39	132
D12–L1	63					52	64	63					52	64
Lumbar	100	34	42	8	77			100	23	42	54	77		
Dis or tumor	51	88		10	96	18		51	18	88	40	96		

Incomplete lesions

	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology	Oldest Normal	Earliest #1 Pathology	Oldest #1 Pathology	Earliest #2 Pathology	Oldest #2 Pathology	Earliest #3 Pathology	Oldest #3 Pathology
Cervical	73	6	47	34		59		57	12	84			10	59
D1–4	56			51				56			51			
D5–8	51	23	364	13	52	28	52	52			364		28	
D9–12	60	48	57	9	21			60	9	57	21		48	
D12–L1	65							65						
Lumbar	79	4	48	46	60	16	71	79	4	60	46	71	16	
Dis or tumor	372	2	35	27	51			372	26	35	27			

An attempt is made to demonstrate when pathological change of each grade first appears and how long after injury do we still find normal appearing kidneys This is further divided into the various levels and whether the neurological lesion is complete or incomplete All numbers indicate *time in months*.

the lumbar group, in that the pathological changes were greater with complete than with incomplete lesions. The reason for this may be the fact that patients with incomplete lesions are more active physically, including ambulation.

c) Incidence of pathological kidney changes in relation to the time element: The earliest time of detection of a grade number 1 was 2 months after injury; the earliest date of observation of a grade number 2 change was 8 months after injury; and the earliest notice of a grade number 3 change was 10 months after injury. There is, therefore, a relationship between the time which has elapsed since injury and the degree of the pathological change. However, this trend does not indicate that the pathological change takes place at that respective date of necessity, because grade 1 was seen as late as 364 months, grade 2 after 150 months, and grade 3 after 174 months. Neither does it imply that changes must take place eventually, since normal kidneys were observed as late as 372 months after trauma (table 3).

d) Comparison of pathological changes in right and left kidneys: The pathological changes in right and left kidneys were as follows:

	RIGHT KIDNEYS						LEFT KIDNEYS					
	Complete			Incomplete			Complete			Incomplete		
Degree of pathology	1	2	3	1	2	3	1	2	3	1	2	3
No. of kidneys	25	17	14	19	10	6	16	18	10	16	7	5
Degree of pathology			1	2	3				1	2	3	
Total No. of kidneys			44	27	20				35	25	15	

It is interesting that the right kidneys showed somewhat more frequent pathological changes than the left. It is also worth mentioning that among six nephrectomies performed during this period, five concerned the right side and that among the 56 patients studied at this Center with vesico-ureteral reflux, 25 cases had bilateral while 19 had right and 12 left reflux; this again points to the right kidney.[3]

DISCUSSION

"More damage to the upper urinary tract occurs in patients whose bladders function poorly."[4] This statement may be slightly too dogmatic, although it has didactic merits for the rehabilitation of cord bladders. In order to explain our point we quote an example from our experience: A patient who had an adequate transurethral resection and alcohol subarachnoid block shortly after injury developed an excellent lower motor neuron type of bladder[1, 2] with 0 residual; yet, bilateral vesico-ureteral reflux and bilateral hydronephrosis developed. We have frequently encountered upper motor neuron bladders, which despite excellent balance developed pathological renal changes. And last, but not least, even patients who were on straight drainage with an intra-urethral catheter, who arrived from another hospital and in whom no attempt has yet been made to create an automatic bladder, developed within the short post-traumatic period of a few months reflux with grade 2 changes. In brief, desirable as it is to attain

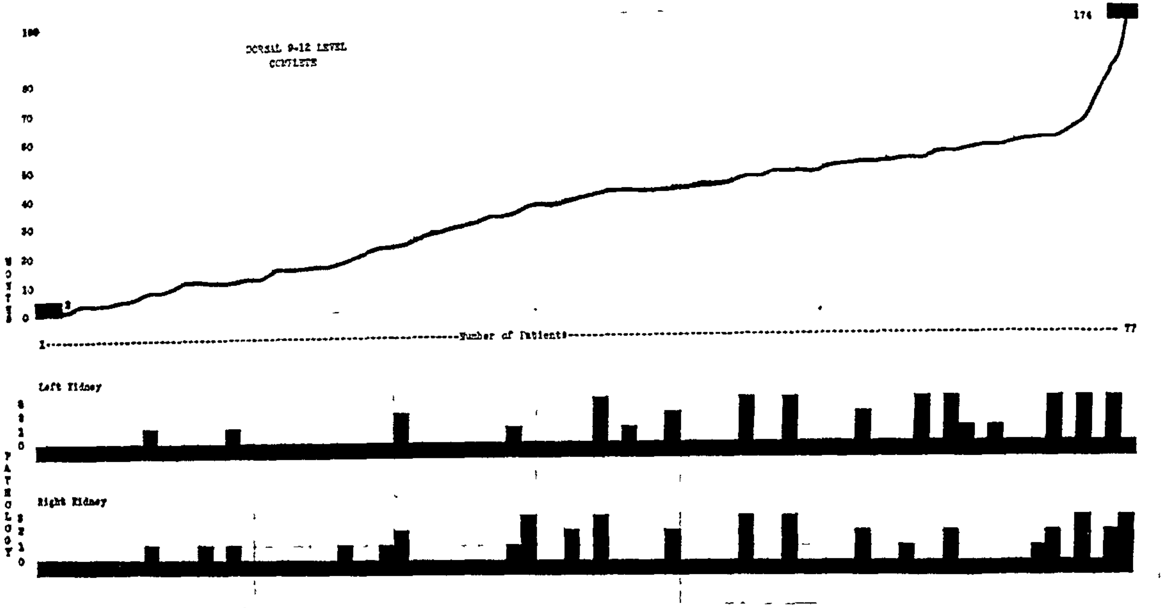

FIG. 2. Effect of time against pathological change found in both right and left kidneys in traumatic group level between dorsal 9–12. Lesions are neurologically complete. Solid vertical black bands represent amount of pathological change. Each block running horizontally represents a patient.

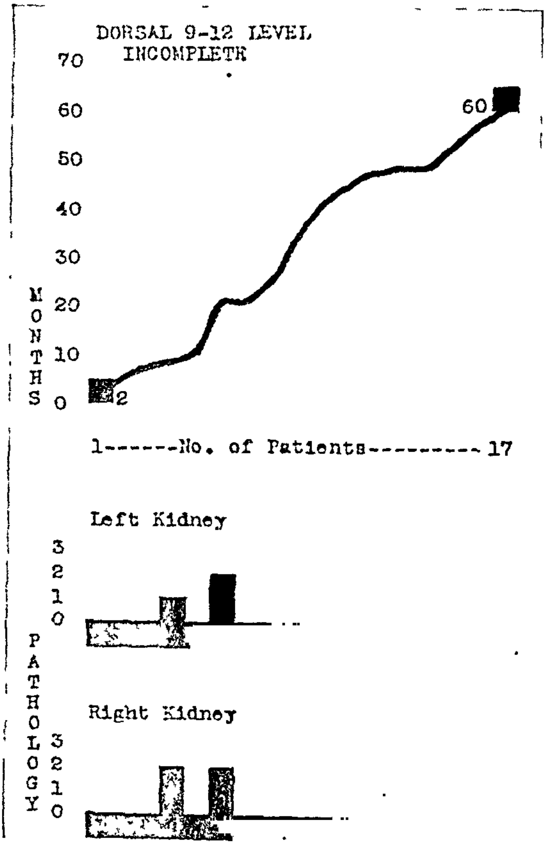

FIG. 3. Similar to figure 2 except that these are incomplete lesions in levels dorsal 9-12.

the goal of a well balanced cord bladder, this *per se* is no assurance that the kidney will stay healthy.

Thus it is impossible to prognosticate the future of kidneys in neurogenic bladders by judging the bladder function alone; this is illustrated by a patient who had a good automatic bladder after 174 months and whose right kidney was a grade 3 lesion whereas the left kidney was normal (fig. 2). Nevertheless it is evident that the time factor plays an important part in increasing the chance for kidney damage (fig. 2).

Six cervical patients in this group had suprapubic catheters, and their kidneys were normal except in one patient who was graded as 1. This corroborates our general clinical impression that most patients with well functioning suprapubic cystotomies are free from frequent pyelonephritic sieges even in the presence of vesico-ureteral reflux. This significant observation will require additional attention and further study.

SUMMARY

The excretory urograms of 315 patients were graded according to a scale which ranged from normal to grade 1, grade 2 and grade 3.

Two hundred and eighty-nine patients had traumatic cord lesions; 26 patients had tumors or a disease of the spinal cord.

Among the evaluated 630 kidneys irrespective of level, completeness or type of cord lesion, and time since injury, 467 kidneys (73 per cent) were essentially normal; 76 kidneys (12 per cent) were graded as grade 1 (mild degree of change); 52 kidneys (8 per cent) were graded as grade 2 (moderate degree of change); and 35 (6 per cent) were graded as grade 3 (severe degree of change, hydronephrosis).

The incidence of pathological changes of the kidney increases with lower lesions.

Pathological changes of the kidney are rather independent of the extent of the cord lesion.

Pathological changes of the kidneys tend to increase with the time elapsed since injury. The earliest grade 1 was seen two months; the earliest grade 2 eight months; and the earliest grade 3 ten months post-injury.

The function of a cord bladder per se does not determine necessarily the future of the kidneys.

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A BACTERIAL CALCULUS IN THE RENAL PELVIS

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A bacterial calculus in the renal pelvis is a rare but interesting finding. This case is the second of its kind in the history of St. Peter's Hospital; the first was reported by Ward in 1926.

CASE REPORT

A woman aged 60 first attended St. Peter's Hospital in September 1952. Her main symptom was pain in the right loin for 6 months. It was of typical renal distribution radiating from the loin down into the groin. There was no frequency of micturition and hematuria had never been noted. She had had two operations on her right kidney in 1910 for renal calculus.

Examination of the patient showed her to be in good general condition. Her cardiovascular, respiratory and nervous systems were normal for her age. An operative scar was noted in her right loin. Both kidneys were palpable. Blood urea was 34 mg. per cent. The following was the report on the examination of urine: Albumin and pus present, film shows numerous gram negative bacilli; on culture there is a profuse growth of B. coli. Excretion pyelography showed both renal shadows to be enlarged, the left one was due to functional hypertrophy. No excretion was visible on the right side but the left kidney was normal in function and structure. No opaque calculus was seen.

The operation of right nephrectomy was performed September 19, 1952. The old scar in the loin was excised. A very adherent kidney was exposed. It was removed but there was considerable difficulty in mobilizing the kidney. The wound was closed with the tube drainage. The kidney was not incised in the operating theater because it is the practice at St. Peter's Hospital to fix all kidneys for three to four days in formalin solution. At the end of that period they are opened by the pathologist, Dr. Cuthbert Dukes.

Convalescence was uneventful and the patient was discharged home 13 days after the operation.

Pathologist's report (Dr. Cuthbert Dukes): The kidney was slightly enlarged, weighed 210 gm. and measured 10 cm. in its long axis. The outer surface was normal except in the region of the junction of the upper and middle thirds, where there was a depressed scar, the site of a previous operation. When the kidney was opened (fig. 1) a very unusual condition was revealed. The renal pelvis was occupied by a solid structure which appeared to be a calculus but was soft and putty-like in consistence and could be easily cut with a knife. It is visible in the photograph as a dark structure in the renal pelvis.

Microscopic examination showed this to be a bacterial calculus composed of masses of gram negative bacilli. The tests for calculi showed the material to be

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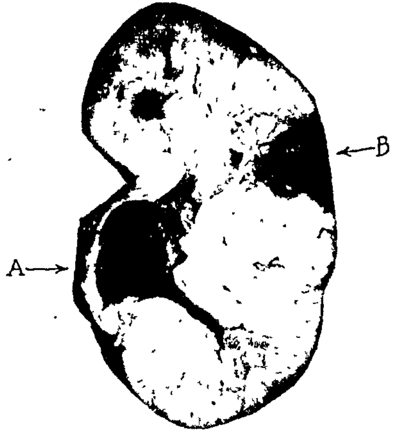

FIG. 1. *A*, bacterial calculus in renal pelvis. *B*, hemorrhage due operative trauma.

organic in character. When sectioned and examined microscopically it was seen to be composed of clusters of bacteria surrounded by and enclosed in a coagulated and fibrinous exudate. The kidney itself was unusual in appearance. In the middle third it was pale in color and no normal markings were visible. Sections from this region showed an advanced stage of chronic pyelonephritis and fibrous tissue replacement with extensive patches of calcification. The dark patch visible at the junction of the upper and middle thirds was hemorrhage due to operative trauma.

COMMENT

Kelly and Dible agree that these cases are rare. They believe that the following conditions are necessary for these calculi to form: 1) some sort of nucleus about which the concretions grow; 2) some cementing process which causes the mass to adhere; 3) circumstances which favor their retention in the renal pelvis during the early stages of their formation.

Although the 3 cases reported by Hyman were all of bacterial calculi in the bladder following suprapubic prostatectomy, he states that they are found more often in the kidney. In his opinion the diagnosis is seldom established before operation. This may be due to the fact that they are not radio-opaque.

Scholl in reporting two personal cases says "continous infection seems necessary."

The patient of Ward passed over a hundred bacterial calculi before operation. The calculi were so soft that they had an easy passage down the ureter. He does not know what factor—"caused the bacteria to cohere and form these very numerous concretions, whilst in other patients infected with the same organism only a bacilluria or urinary infection results."

In presenting this case report I should like to lay emphasis on the value of preserving kidneys after removal for three to four days in formalin solution before examining them. I believe that had this kidney been incised in the operating theater the calculus might have been mistaken for a blood clot and so an interesting pathological specimen would have been lost. It was the observation that the calculus was cut so easily with a knife which raised the query that it might be a bacterial calculus.

SUMMARY

A case of a bacterial calculus in the renal pelvis is reported.

A plea is made for the preservation of removed kidneys for three to four days in formalin solution before dissecting them.

This case was shown at a meeting of the Urological Section of the Royal Society of Medicine and I wish to thank the Council for permission to publish the case. In addition I beg to acknowledge the valuable help I received from Mr. Harland Rees and Dr. Cuthbert Dukes in the preparation of this article.

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RENAL PAPILLARY NECROSIS: A CLINICOPATHOLOGIC STUDY

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The scarcity of papers in the urologic literature dealing with renal papillary necrosis has prompted the submission of this report. A revival of interest in renal papillary necrosis followed Gunther's report[1] in 1937 correlating this pathologic entity with diabetes mellitus. Mandel[2] has recently summarized the numerous case reports, few of which were diagnosed clinically. At the Indiana University Medical Center, 6 cases of renal papillary necrosis have been recognized since 1945; two of the patients survive and four are deceased. These 6 cases form the basis of this study.

INCIDENCE

As summarized by Mandel in 1952, 160 cases have been recorded in the available literature since 1877, when first described by von Friedreich.[3] Ninety-six of these cases were associated with diabetes mellitus, whereas 64 were apparently nondiabetic. Obstruction of the urinary tract was present in 63 and absent in 97. It is significant that only 16 had neither diabetes mellitus nor urinary tract obstruction. In two series of autopsied diabetics, the incidence of papillary necrosis has been 3.37 per cent and 4.75 per cent.[4, 5] In these series of diabetics about one fourth succumbing to acute pyelonephritis have had papillary necrosis. The incidence of this entity in urinary tract obstruction is so small that no accurate statistics have been established.

Female diabetics are prone to have papillary necrosis twice as frequently as their male counterparts, whereas in nondiabetics the males outnumber females six to one. This incidence is presumably due to the greater incidence of urinary obstruction in men. The majority of both diabetic and nondiabetic patients with this lesion are over 50 years of age. The lesion was bilateral in 61 of 160 cases reviewed by Mandel.

DIAGNOSIS

Renal papillary necrosis must be suspected in any diabetic with severe acute pyelonephritis, gross hematuria, renal colic, micturition of solid material, or rapidly progressive renal insufficiency not responsive to chemotherapy and diabetic management. The disease may be an acute, fulminating, rapidly fatal process, or it may be relatively chronic and progressive, with or without intermittent or terminal acute, fulminating episodes.[2, 4, 5, 6, 7] Oliguria and anuria may occur. The severity of the diabetes does not seem to be a factor.[5]

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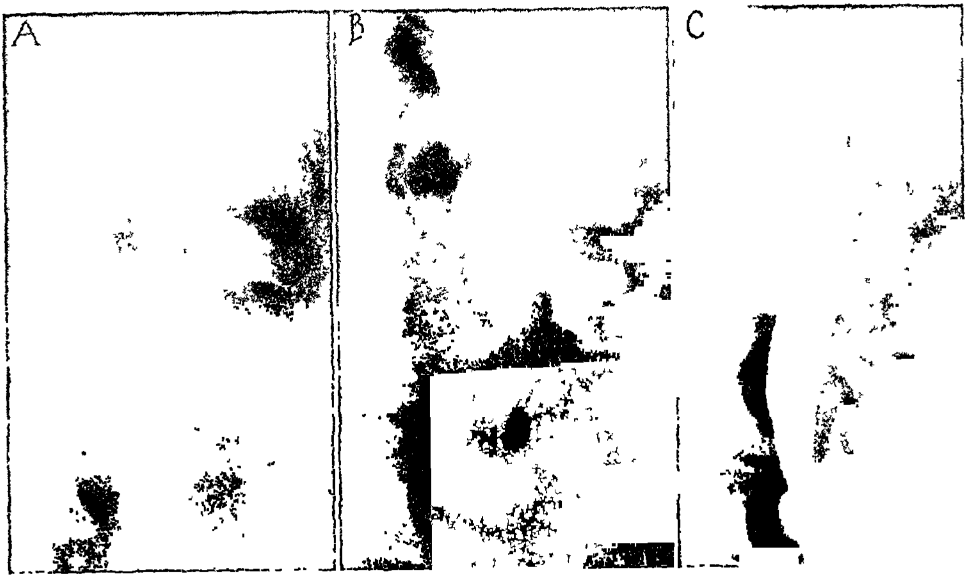

FIG. 1. *A*, case V. C. "Ring shadow" is evident in superior calyx in left retrograde pyelogram. Papilla lies separated in calyx. *B*, case V. C. Six weeks following A, sloughed papillas leave clubbing on left. *C*, case M. W. Late results as noted by pyelography of left kidney 2 weeks before death. Note both clubbed and ragged calyces. Cortical abscesses also found at autopsy.

Gross hematuria may denote the slough of a papilla. The line of separation between necrotic papilla and viable medullary parenchyma is the site of hemorrhage. Hematuria is often severe, with the passage of vermiform clots.

Renal colic indicates obstruction of a major calyx or ureter by sloughed parenchyma or by blood clot. Obstruction may exist to a high degree.

The passage of a papilla in the urine is of course a dramatic event. This is a rather rare phenomenon, many such masses either being overlooked or undergoing liquefaction necrosis prior to their excretion. Such solid masses that are passed and submitted to the physician are conclusive evidence when examined microscopically.

More difficult of identification are those diabetics whose renal function progressively fails. Many diabetic patients with pyelonephritis in whom papillary necrosis is not found will tend to follow this fatal course. Only an omnipresent awareness of the possibility of such a necrotic reaction will bear diagnostic fruits.

Roentgenographic study must often be utilized. The retrograde pyelo-ureterogram may be helpful, if not diagnostic. Early changes noted are those of ragged irregularities reminiscent of renal tuberculosis,[8] usually selective of one or two minor calyces. Later, separation of the papilla will leave a "ring shadow" in the calyx (fig. 1, *A*). A negative filling defect within the pelvis indicates the passage of the papilla into the collecting system. The calyx, deprived of its papilla, displays a clubbed appearance not unlike that seen in hydronephrosis. In this clubbing, however, pelvic dilatation is not found. It should be emphasized that the so-called "ring shadows" and pelvic defects due to loose papillae at pyelography are extremely uncommon. In pyelographic studies more frequently one notes end-results of sloughing. Here typically are seen clubbed minor calyces in the absence of obstruction. Many such patterns are overlooked, simple pyelonephritis being advanced as the diagnosis. These findings are illustrated in figure 1, *B* and *C*.

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[8] Harrison, J. H. and Bailey, O. T.: J.A.M.A., **118**: 15, 1942.

The clinical diagnosis of papillary necrosis in the nondiabetic is an even more difficult problem because of its relative rarity. Only familiarity with the typical roentgenographic picture and careful histologic study of tissue fragments submitted by the patient will lead to the diagnosis. The vast majority of these cases, diabetic or nondiabetic, reach the autopsy table before papillary necrosis is suspected.

CASE REPORT

A 43-year-old white housewife was admitted to the Indiana University Medical Center for the first time on November 17, 1951 with complaints of nausea, vomiting, and mild malaise for 2 weeks. The patient was a known diabetic, taking insulin and a diabetic diet. One month before admission a diagnosis of pyelonephritis was made by her local physician, and a series of furuncles was reported 2 weeks later. Known hypertension of 4 years' duration was the only other significant feature of this history. The physical examination was entirely normal except for a blood pressure of 158/90.

Significant laboratory studies included a urine concentration of 1.010 with a faint trace of albumin and 3 plus pyuria. Hemoglobin was 9 gm. with 3.01 million red cells. White cell count and differential were normal. The admission nonprotein nitrogen was 55 mg. per cent; phenolsulfonphthalein tests revealed 13 per cent excretion in 15 minutes, and a total of 31 per cent in 30 minutes. Escherichia intermedium was obtained on urine culture. Fasting blood sugar was 250 mg. per cent. Excretory urography demonstrated no visualization, and retrograde pyelography revealed a filling defect in the left pelvis with blunting of the calyces. The

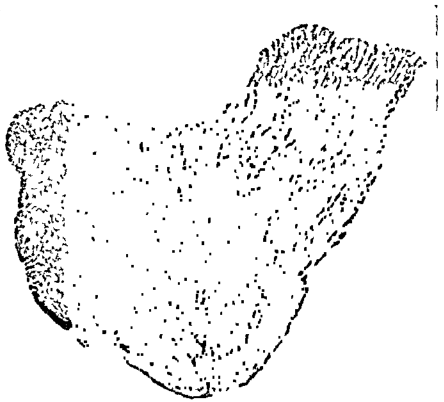

FIG. 2. Case V. C. (S.P. 64767). Low power. Necrotic papilla recovered from urine

patient was placed on terramycin and made a satisfactory response prior to discharge.

The patient was followed in the clinic, and made satisfactory progress except for intermittent episodes considered to be pyelonephritis with left renal colic. Antibiotic therapy was used intermittently. On April 15, 1952, the patient reported passing a small piece of tissue in the urine and brought this specimen to the clinic. She was subsequently re-admitted on April 17, 1952 with the tentative diagnosis of papillary necrosis. In addition, she reported a recent history of gross hematuria. Physical examination was unchanged except for blood pressure of 180/95. Again the urine showed a faint trace of albumin and pyuria. Her diabetic control was entirely satisfactory. Retrograde pyelography demonstrated left hydronephrosis, and subsequent films led to the diagnosis of papillary necrosis.

The specimen passed by the patient consisted of two pieces of tissue which were grayish-white and friable. The larger measured 2.0 by 1.0 by 3.0 cm. and the smaller about 5.0 mm. Microscopically the sections showed a necrotic papilla in which the outline of tubules was visible (fig. 2).

Again the patient was given antibiotics and made a satisfactory response prior to discharge. As an out-patient, she continued to report bouts of frequency, burning, gross hematuria and, for the first time, right flank pain. Antibiotics were used intermittently, and on July 28, 1952 the patient was re-admitted. She appeared acutely ill and complained of severe right flank pain necessitating narcotics. Temperature was 103F, and marked right costovertebral angle tenderness was present. Blood pressure was 76/42. The blood sugar was essentially normal; CO_2 combining power was 21 m/Eq., nonprotein nitrogen was 65 mg. per cent. Albuminuria, pyuria, and hematuria were again noted. A right ureteral obstruction was relieved by catheterization. She received terramycin, penicillin, and symptomatic care; again she made a satisfactory response and has been followed as an out-patient, remaining asymptomatic.

ETIOLOGY

The appearance of the lesions of papillary necrosis is that of infarction of the papilla, with or without superimposed infection. The pyramids derive their blood

FIG. 3. Case M. N. (S.P. 41083). Gross appearance of cross section of kidney showing necrotic papilla partially detached.

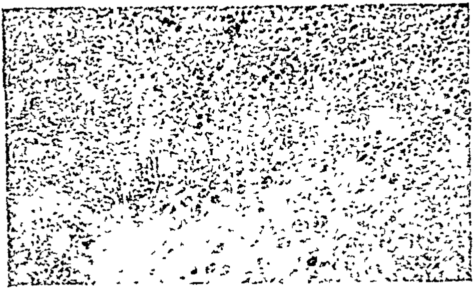

FIG. 4. Case E. R. (autopsy 12151). Low power. Sharp line of demarcation between viable and necrotic tissue. Note capillary thrombi in viable portion.

supply from branches directly from the arcuate arteries. Vessels arising as continuations of efferent arteries from the juxtamedullary glomeruli (Trueta shunt) may also be present. These vessels are susceptible to occlusion by pressure as well as thrombosis in certain disease states. Occlusion of these vessels does not impair the blood supply to the columns of Bertini or the cortex, and these structures are spared in papillary necrosis.

In necrotizing papillitis, occlusion of the vessels supplying the pyramids may be brought about in several ways, as evidenced by clinical and experimental studies. Multiple thrombi in vessels of the pyramids are occasionally seen in human cases, and were produced in a dog and in rabbits by Mandel and Popper[9] by the injection of vinylamine. In many human cases, multiple thrombi are absent.

The compression of vessels by inflammatory edema may be an important mechanism in the production of these lesions. Most patients with papillary necrosis have acute pyelonephritis, in many instances to a severe degree. The photomicrographs of reported cases and our own material reveal a marked degree of edema accompanying the inflammatory reaction. The causative organism probably is not important except for the degree of edema it excites. The organisms reported include Klebsiella pneumoniae, streptococci of the viridans type, tubercle bacilli, and actinomyces, but Micrococcus pyogenes var. aureus and Escherichia coli have been encountered most frequently. The role of the lowered pH suggested by Edmundson,[4] citing the work of Menkin, may be important in that it helped increase the edema.

That other vascular diseases of the kidney, such as arteriolonephrosclerosis and intercapillary glomerulosclerosis, play a role in the development of these lesions is suggested by their frequent occurrence in reported cases. The already-embarrassed circulation would appear to be more susceptible to further insult.

The presence of para-amyloid in some cases of papillary necrosis was assigned a significant role by Mellgren.[10] Here again, a taxed blood supply was probably more susceptible to added injury.

Obstruction of the urinary flow has been important in clinical cases, especially

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[9] Mandel, E. E. and Popper, H.: Arch. Path., 52: 1, 1951.

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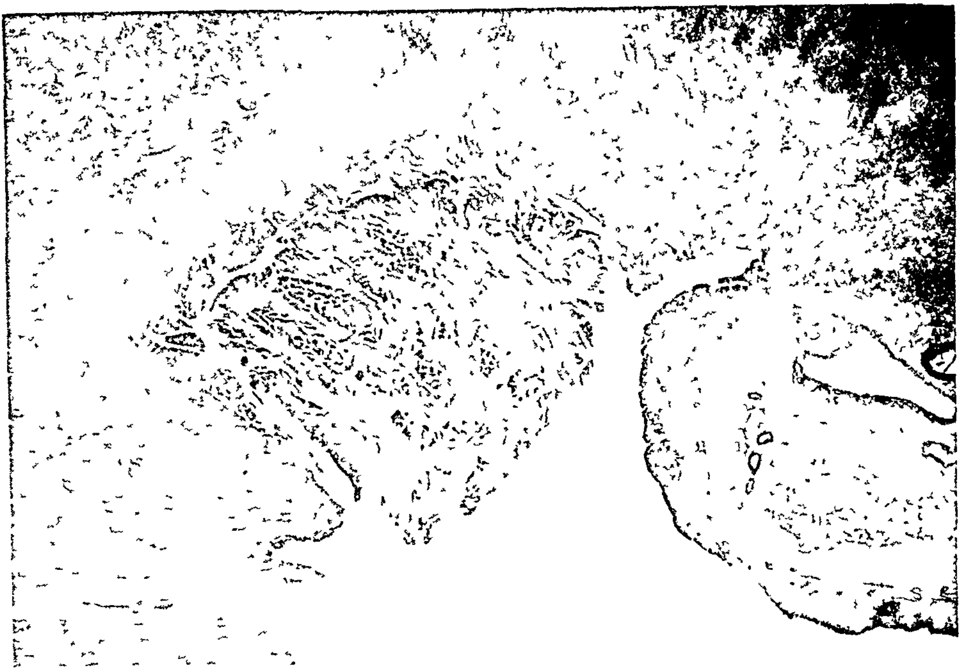

FIG 5 Case M. N (S P 41083) Low power Almost complete separation of necrotic papilla This stage would be represented as "ring shadow", as noted in figure 1, *A*

in nondiabetic males. Muirhead[11] felt that the increase in intrapelvic pressure produced in his animals (dogs) was sufficient to occlude the medullary vessels, with the development of necrotizing papillitis. In human cases obstruction not only raises the intrapelvic pressure but also potentiates infection.

PATHOLOGY

The degree of papillary necrosis varies in the same kidney and from case to case. There may be necrosis of the entire papilla (fig. 3) or part thereof. Frequently, even when only a part of the papilla is involved, the necrosis extends from the base to the tip, and usually located laterally. The necrosis is of the coagulative type, and there is a sharp line of demarcation at the junction with viable tissue (fig. 4) Grossly the necrotic part may be yellow, green, or dark red. Occasionally there are capillary thrombi along the border of necrosis (fig. 4); usually there is edema of the interstitial tissue; less frequently there is cellular infiltration. As the lesions progress, the necrotic zone sequestrates, the line of cleavage being a sharp one starting at the lateral border of the base of the papilla and working centrally, so that the last point of juncture is usually in the midportion (fig. 5). The columns of Bertini remain uninvolved. As the papilla separates, the interstitial tissue at the base is infiltrated with wandering cells, especially plasma cells and lymphocytes. When the separation is complete the border is sharp (fig. 6, *A*). The necrotic papilla lies free in the pelvis (fig. 6, *B*). In addition there may be varying degrees of arterio- and arteriolar sclerosis, and pyelonephritis. Abscesses are frequently, but not always, present (fig. 6, *B* and *C*).

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[11] Muirhead, E E , Vanatta, J and Grollman, A · J A M A , **142:** 627, 1950

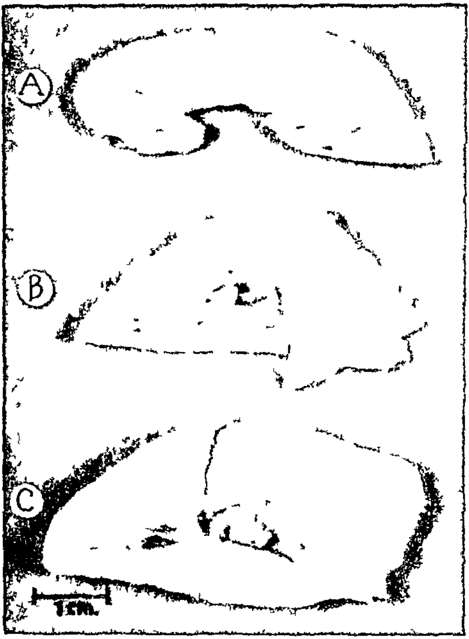

FIG 6 Case M W (autopsy 13035) Gross appearance of kidney on cross section showing varying stages *A* appearance after papilla has been sloughed leaving clean line of separation This would be represented as clubbed calyx as noted in figure 1, *B* and *C* *B* and *C*, partially separated papillae are evident Abscesses of the kidney are present

MANAGEMENT

There is a paucity of published information on the management of papillary necrosis To be sure, infection is the dominant and immediate problem at hand It must be emphasized that careful bacteriologic studies of the offending organisms are imperative These should include drug sensitivity tests with *all* the available antibiotics Inasmuch as the rapidity of renal destruction is often alarming, potent antibiotic therapy must be brought to bear promptly

Enhancement of existing renal infection as well as hydronephrotic destruction of renal parenchyma must be avoided Blockage of the drainage channels with sloughed tissue may be a serious problem, ureteral catheter drainage *may suffice* temporarily Irrigation of the pelvis and ureter with streptokinase streptodornase may cause rapid lysis of the sloughed tissue Surgical intervention for obstruction unrelieved by such conservative methods may conceivably be necessary

Nephrectomy has been advocated and may be life saving However, careful consideration of medical management, the exclusion of the existence of bilateral disease, and evaluation of total renal function, must precede any decision for

TABLE I

Case	V C	E R.	M W.	H. H.	M. N.	D. P.
Age	43 years	21 years	50 years	48 years	58 years	78 years
Sex	Female	Female	Female	Female	Female	Female
Diabetes duration	9 years	14 years	2 months +	1 year	Unknown	None
Daily insulin requirements	30 units	80 units	13 units	*Unknown*	25 Units	—
Urinary obstruction	No	No	No	No	No	Bilat
Hypertension	Yes	No	No	No	No	No
Azotemia	Yes	Yes	Yes	Yes	Yes	Yes
Hematuria	Yes	Yes	Yes	Yes	Yes	Yes
Pyelonephritis	Yes	Yes	Yes	Yes	Yes	Chronic
Bacteria	E intermedium, E. coli	E coli, non hemolytic streptococci	Hemolytic streptococci., P. vulgaris, Staph aureus	Hemolytic streptococci., A. aerogenes, E. freundii	Unknown	Unknown
Bacteremia	E coli	E coli, hemolytic streptococci	No	E. coli	Unknown	Unknown
Other renal disease	*	†	†	‡	Unknown	—
Diagnosed	Tissue from urine	Autopsy	Autopsy	Autopsy	Surgical specimen	Autopsy
Unilateral or bilateral	Bilat (?)	Bilat.	Bilat.	Unilat.	Unilat.(?)	Bilat.
Duration to death . .	*Living* 1½ *years* later	2 months	4 weeks	5 weeks	*Living* 2 *years* later	Unknown

* Pyonephrosis (last admission)

† Intercapillary glomerulosclerosis

‡ Hypoplasia of one kidney

extirpation of renal parenchyma Effective antibiotic therapy may eliminate or postpone nephrectomy Certainly nephrectomy is contra-indicated if the integrity of the opposite kidney is in question

DISCUSSION

Our 6 cases (table 1) closely parallel those previously reported All demonstrated dysuria, hematuria, chills, fever, nausea, and vomiting Four of the six reported characteristic renal colic Three showed porstration and stupor, and two were in coma It is interesting to note that all but one were diabetic females without urinary tract obstruction, and that the severity of their diabetes, as measured by the daily insulin requirements, varied from 13 to 80 units per day Four of the patients were in the 40 to 60 year group, whereas one was only 21 years old, the latter being younger than those generally reported The diagnosis of acute pyelonephritis was made in all cases, and the organism or organisms were established in four In three, bacteremia was confirmed by blood culture In contrast with some reports, hypertension was found in only one patient The presence of concomitant renal disease is noteworthy Two of the four patients studied at postmortem examination had intercapillary glomerulosclerosis

Bilateral papillary necrosis was confirmed in three patients and unilateral involvement in one In the fifth, it was assumed but unproven that the disease was unilateral, whereas x-ray evidence was conclusive of bilateral disease in the sixth Four of our patients manifested the typical fulminating and rapidly fatal course of this entity, but it is perhaps significant that two of them are living and apparently well 1½ and 2 years later

In one of our cases, reported in detail, the diagnosis was established antemortem by histological study of tissue obtained from the urine We have found only five similar cases in the literature

Careful consideration of the sequence of pathogenesis is the key to pyelographic diagnosis in this lesion Ragged calyces, ring shadows, and clubbing of the calyces all have their counterpart in pathologic material

SUMMARY

Papillary necrosis must be suspected in diabetics with severe renal infection or renal failure

The diagnosis can be confirmed by histologic examination of sloughed tissue or pyelographic studies showing ring shadows Ragged or isolated clubbed calyces are strongly suggestive of this lesion

Nephrectomy in the acute unilateral disease may be beneficial In bilateral disease, diabetic control, antibacterial therapy and promotion of free urinary drainage are the only courses of action available

Six cases of papillary necrosis are herein reported, one in detail

The photographs were prepared by Mr James F Glore of the Department of Illustration

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CONGENITAL SOLITARY PELVIC KIDNEY. A STUDY OF ITS BLOOD SUPPLY BY AORTOGRAPHY

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The principal anatomical features which distinguish the congenital ectopic kidney from the ptosed kidney, i.e. a kidney that has wandered from its normal place, are its short ureter and the low origin of its blood supply. These vessels may originate from the lower few inches of the aorta or from the large vessels in the true pelvis.

Ectopic kidneys have been classified by their position. Eisendrath and Rolnick (1938), for instance, divided them into the following groups: 1) low lumbar, between normal position and the fifth lumbar vertebra; 2) iliolumbar, across the crest of the ilium; 3) iliac, in the iliac fossa; 4) iliopelvic, at the level of the brim of the true pelvis; 5) pelvic, within the true pelvis.

Transitional types have also been encountered. Judging by the literature some workers have included the iliac or iliopelvic kidney in the group of "solitary pelvic kidney".

A solitary pelvic kidney is very rare. According to Stevens (1937) it is met with once in approximately 22,000 autopsies. Beneventi (1950) collected 43 cases from the literature and added a case of his own. We have traced a further 21 cases in the literature which, together with the case now presented, bring the total number of reported cases to 66 (table 1).

An understanding of the blood supply of the ectopic kidney rests on the knowledge of renal embryology. The kidneys appear first in the true pelvis as two buds, which arise from the wolffian ducts and the distal parts of the wolffian bodies. They form the metanephros at this stage. During the process of development the kidneys migrate upwards. A temporary blood supply is received from the internal iliac artery, common iliac artery, neighboring vessels or from the aorta. The permanent blood supply is not acquired until the kidneys have reached their normal position, which occurs at the end of the second month of intra-uterine life when the embryo is in the 25-30 mm. stage. If the kidneys do not migrate upwards or their ascent is arrested, the temporary blood supply then becomes the permanent one. The origin of the vascular supply of the ectopic kidney shows great variety.

CASE REPORT

Hospital record No. 727/52, a girl, aged 16 years, sought medical advice because of amenorrhoea. Otherwise the past history was irrelevant. The attending physician discovered a mass in the true pelvis, which he suspected to be a hematometra secondary to aplasia of the vagina, and referred the patient to our clinic for treatment.

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TABLE 1. *Sixty six cases of single ectopic kidney published up to 1952*

Year	Author	No of Cases	Year	Author	No of Cases
1927	Idel	1	1949	Beneventi	1
1935	Riley	1	1949	Keitzer and Riemen Schneider	1
1935	Spirt and Spectorowa	1	1949	Cowen	1
1938	Fuchs	1	1949	Nalle, Crowell and Lynch	1
1945	Nation	1	1949	Cokely and Webster	1
1946	Schreiber and Smith	1	1949	Wall and Lowry	1
1946	Mays	1	1949	Berg and Kearns	1
1947	Hanly and Steel	2	1949	Hanbury	1
1948	Brady	1	1949	Kunstadter and Shapiro	1
1949	By Beneventi collected from the literature in the years 1830-1949	43	1950	Hawes	2
			1950	Diamantis	1
			1952	Borell and Fernstrom	1

Condition on admission. The secondary sex characteristics were normally developed. Gynecological examination revealed absence of the vagina. On rectal examination a mass the size of a goose egg was palpated fairly high up in the true pelvis just to the left of the midline, it was somewhat adherent, tender, and softer to the touch than a normal uterus. The mass was suspected to be hematometra. In view of the fact that it was not possible to establish a definite diagnosis percutaneous retrograde arteriography of the iliac artery was carried out for further information, using the method described in a previous paper (Borell et al., 1952).

Arteriographic findings. The right uterine artery was absent. A vessel was seen arising from the extreme proximal end of the left internal artery and running downwards and medially, its course was remarkably straight (fig. 1). Within an area corresponding to the site of the mass, it divided into several small branches. We believed the vessel to be a uterine artery, whose appearance and course deviated from the normal.

The first step in the treatment of the patient was surgical reconstruction of the vagina by the methods described by Kirchener-Wagner. Two months later laparotomy was performed for information about the nature of the mass. It was found to be retroperitoneal, and was a pelvic kidney. A short ureter extended from the center of the lower pole of the kidney laterally to the left and downwards. No normally placed kidneys were palpable. The right adnexa and the uterus were absent. The left ovary was normal in size and contained follicles. The appearance of the ampulla and the fimbriae of the left fallopian tube was normal. The tube measured about 4 cm. in length and terminated in a short strand of connective tissue.

The findings at laparotomy led us to re-examine the arteriogram. In doing so we found that the shadow of the lower pole of the left kidney was visible. The film had been taken about 5 seconds after injection of the opaque medium. Hence, the vessel which we had believed to be the uterine artery (fig. 1) was in fact the renal artery.

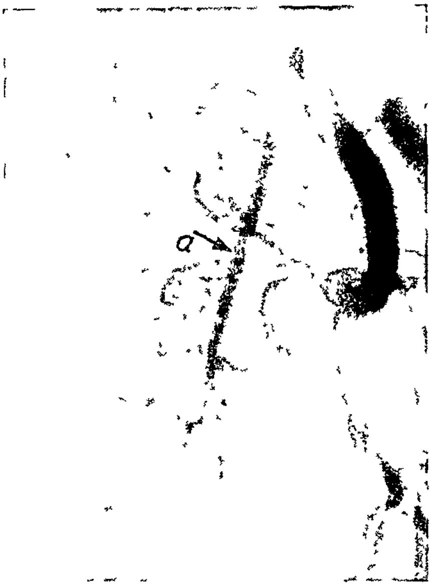

FIG 1

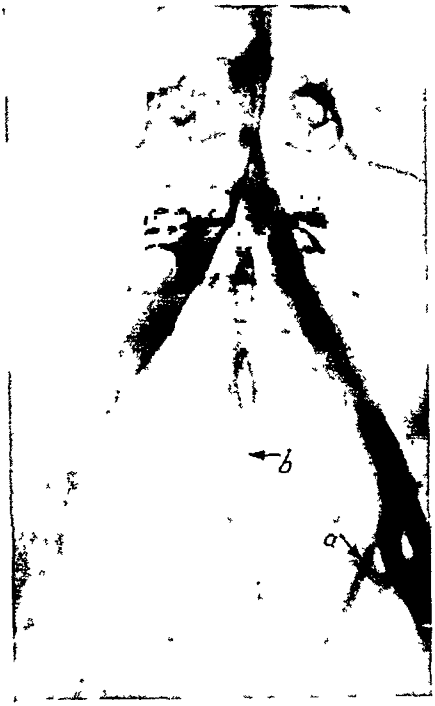

FIG. 2

FIG. 1 Retrograde arteriography, injecting left femoral artery. *a*, Vessel extending to and supplying lower pole of pelvic kidney.

FIG 2 Aortography, introducing catheter percutaneously into aorta through femoral artery Blood supply of pelvic kidney is shown. *a*, Vessel arising from left internal iliac artery. *b*, Vessel arising at bifurcation of aorta

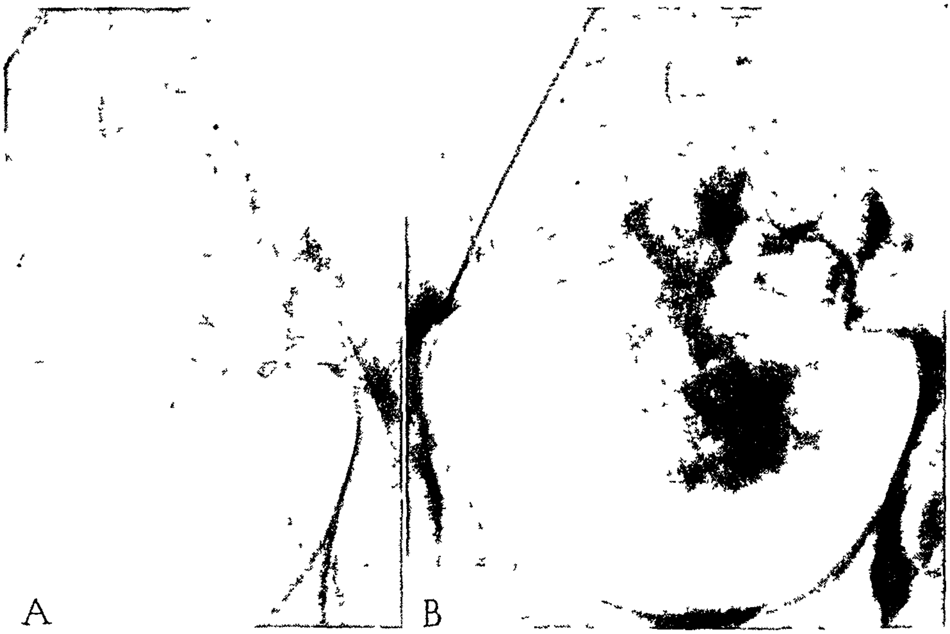

FIG. 3. Aortography, introducing catheter percutaneously into aorta through femoral artery. Blood supply of pelvic kidney is shown. *A*, same vessel as seen in figure 2. Parenchyma of kidney is faintly visible *B*, film taken 4 seconds after film *A*. Parenchyma of kidney is now clearly visible Shape and position of kidney are well shown.

Cystoscopy: The trigone was symmetrical. The orifice of the right ureter was absent, that of the left ureter was clearly visible and opened and closed rhythmically.

Excretory urography: No renal outlines were visible: nor was any opaque medium seen in the area corresponding to the normal position of the kidneys. A renal pelvis was seen in front of the sacrum. The calyces were directed to the left and upwards. A short ureter extended to the left side of the bladder, entering it in the normal position.

Aortography: This examination was made for information concerning the exact position, shape and blood supply of the ectopic kidney, using the technique described by Seldinger (1953). With this method the catheter is introduced percutaneously into the femoral artery. The aortogram disclosed that two blood vessels supplied the pelvic kidney: a large one, arising at the bifurcation of the aorta, and a smaller one, originating from the left internal iliac artery (figs. 2 and 3, *A*). As the parenchyma showed up well it was possible to determine the shape and position of the ectopic kidney (fig. 3, *B*).

DISCUSSION

In the 65 cases of congenital solitary pelvic kidney published, the anatomical characteristics of the blood vessels supplying the malplaced kidney have been fully described only in 9 cases from autopsy findings. As far as we are aware, the case presented is the only one in which these vessels were investigated *in vivo* by aortography. Figure 4 shows a schematic representation of the blood supply of the ectopic kidney in these 9 cases, and in the case presented. The origin of the blood vessels supplying a solitary pelvic kidney appears to vary greatly. The vessels may arise from the internal iliac arteries, the common iliac arteries or from the aorta.

These 10 cases may be grouped according to the origin of their vascular supply as follows: 1) from the common iliac artery, 2 cases, 2) by a vessel arising from the internal iliac artery and the aorta or by a vessel originating from the common iliac artery and the aorta, 3 cases, 3) by a branch of the aorta, i.e. a vessel arising at the bifurcation of the aorta, 2 cases, 4) by several vessels arising at different levels in the aorta, 2 cases.

It may reasonably be assumed that a relationship exists between these variations in the origin of the blood supply and the different stages in the upward migration of the kidneys. The cases of group 1 and 2 probably illustrate early stages of this process while those included in group 3 and 4 most likely exemplify later stages. The case published by Hebb (1885), in which the solitary ectopic kidney derived its blood supply from two branches of the right internal iliac artery and from three branches of the aorta, does not fit in any one of the above groups.

We should have liked to investigate the question whether or not a relationship exists between the position of the ectopic kidney and the source of its blood supply. Such an investigation was unfortunately not possible because of incomplete information about the exact position of the ectopic kidney in most cases published.

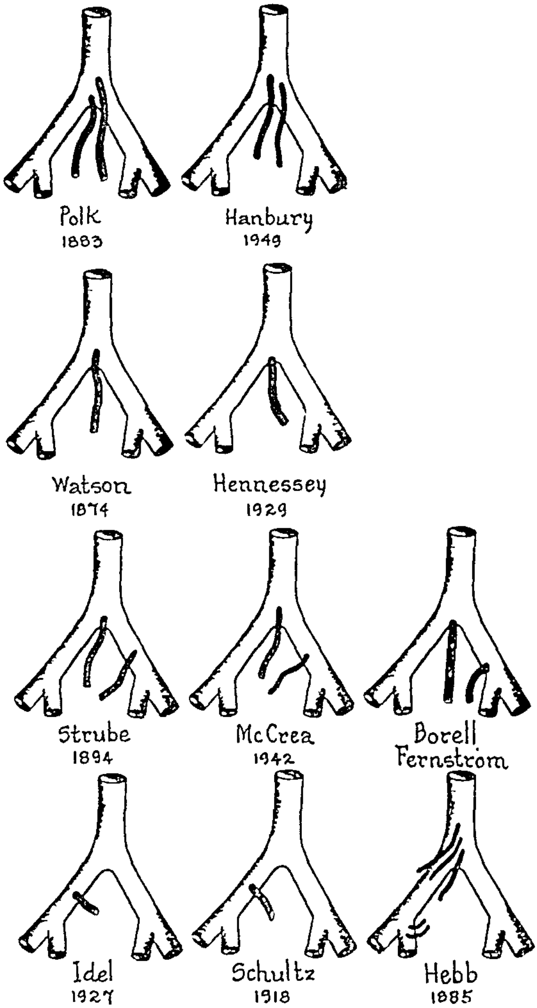

FIG. 4. Schematic representation of blood supply of solitary pelvic kidney.

The incidence of solitary pelvic kidney in women and men is practically equal. Of the 66 cases discussed (including the case presented) information about the sex of the patient was available in 52 cases. Of these 27 were women, and 25 were men. The association of pelvic kidney and anomalies of the genitalia is rare in male patients. If it does occur undescended testes are then generally present.

According to Nalle and collaborators (1949), a solitary ectopic kidney in women is always associated with an anomaly of the reproductive organs. Many workers believe that the close embryological association between the müllerian and wolffian ducts accounts for the frequency of this association. In the 27 female cases published, a more exhaustive medical examination might have revealed an anomaly of the reproductive organs in 4 cases. With the exception of the case reported by Hennessey (1929) an anomaly of the reproductive organs, however, co-existed in the remaining 22 cases. The anomalies found were as follows: aplasia of the vagina, 17 cases (including the case presented) or 71 per cent; aplasia of the uterus, 9 cases; absence of the right fallopian tube, 4 cases; absence of the left fallopian tube, 9 cases; absence of the right ovary, 2 cases; absence of the left ovary, 7 cases.

If aplasia of the vagina is associated with a mass in the true pelvis the nature of which cannot be determined clinically, it is imperative that the urinary tract be carefully examined with regard to a renal anomaly or disease before attempting vaginoplasty. In several cases of solitary pelvic kidney reported in the literature the renal anomaly was thought to be the uterus or an ovarian tumor and laparotomy was carried out.

Reversely, if urological examination discloses a pelvic kidney the reproductive organs should also be carefully examined.

The diagnosis of renal ectopia may be difficult. Early diagnosis, however, is of greatest importance, because an ectopic kidney is easily infected with subsequent calculus formation.

Retrograde urography may give rise to complications in cases of solitary pelvic kidney because hydronephrosis, pyelitis or stones occur in these patients more frequently than in patients suffering from some other renal lesion. By excretory urography, again, unsatisfactory pictures are often obtained because of failure to achieve sufficient ureteric compression. We feel that aortography offers great advantages in such cases, provided that renal function is not impaired. Aortography, carried out by the method described, is a harmless procedure and does not cause any noteworthy discomfort to the patient. Moreover, it provides information about the blood supply, shape, position and function of the ectopic kidney.

With aortography the opaque medium readily enters the parenchyma of the ectopic kidney with satisfactory filling of the renal pelvis and the ureter as a result. In most cases thus examined further examination by retrograde urography will probably not be required.

The diagnostic value of aortography in cases of renal ectopia has been emphasized by Doss (1946), Griffith (1950) and others. We feel that aortography should also be carried out in cases in which there is a unilateral diseased ectopic kidney and a normal kidney on the other side. The removal of a pelvic kidney may be difficult, technically, because of adhesions and the abnormal blood supply. Excessive hemorrhage may be encountered at operation. Knowledge of the anatomy of the blood vessels supplying the diseased kidney will, no doubt, facilitate the operation. Information about the anatomical features of the renal vessel will also be of value in the rare cases, in which nephropexy is contemplated.

SUMMARY

A case of congenital solitary pelvic kidney associated with aplasia of the vagina, uterus, and the right adnexa is reported. The blood supply of the pelvic kidney was studied by aortography. The source of the blood supply was compared with that in the 9 cases reported in the literature in which information on this point was given. The value of aortography in cases of renal ectopia is emphasized.

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HYPERNEPHROMA IN SEVEN-YEAR-OLD WHITE GIRL

JAMES W BEATTIE

Only four cases of hypernephroma in the young are registered in the American Tumor Registry . ages 6, 13, and two at 14 years Only one, a 14-year-old boy, was alive 6 months after nephrectomy Campbell,[1] after mentioning the above, further emphasizes the rarity of this tumor in childhood, citing a single instance of its occurrence, in a 7-year-old boy, in 52 cases of renal tumor in childhood collected in New York hospitals (1937) According to Gross,[2] none have been encountered in 30 years at Boston Children's Hospital Bell[3] states he is not convinced that adenocarcinoma of the adult type ever occurs in children, citing the article of Hellstrom[4] in which hypernephroma in a child of 18 months was described but no microscopic illustration was given Scotti[5] reports in a series of cases from the New York Post Graduate Medical School and Hospital 3 cases (ages 6 months, 4½, 6½ years) diagnosed as primary carcinoma of the kidney, all of which have been checked by competent pathologists In a review of 367 cases by Cathcart,[6] only one case less than 21 years of age is listed, a 14-year-old boy

This patient (E S) was admitted to St Anthony Hospital, Las Vegas, New Mexico April 16, 1951, having been seen in the office 6 weeks previously, for the first time Then he had pertussis, in addition to a right upper abdominal mass Treatment was necessary for that infection before she could be admitted to the hospital for studies The mother gave a history of the child having had a fall the previous September, at which time a small mass was noted in the right abdomen There had been no gastro intestinal symptoms and no noticeable weight loss The child had attended school until she developed pertussis, and had not been bothered by the abdominal mass in the least There had been some gradual enlargement of the tumor, but the patient's parents paid little attention to it

Examination at the time of admission to the hospital revealed a well-developed, fairly well-nourished, white child Head and neck were normal except for a few small discrete lymph nodes in the neck The chest was clear and no abnormality was noted on radiographic examination The heart was entirely within normal limits Abdominal palpation showed nothing abnormal except a nontender, firm, slightly movable mass occupying a position slightly to the right of the midline in the upper midportion of the abdomen, approximately 8 by 10 cm Examination otherwise was completely within normal limits

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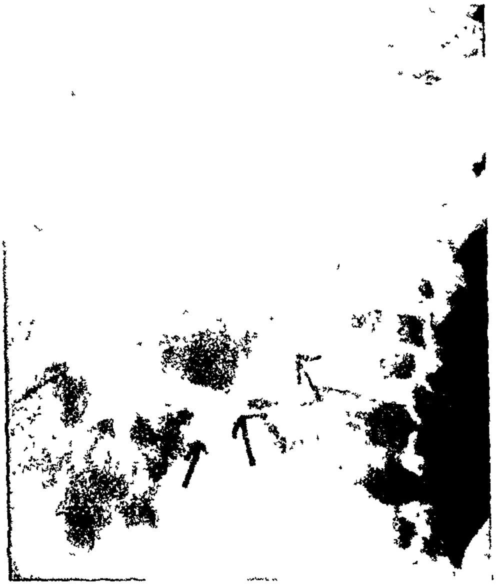

FIG. 1. Excretory urogram showing relative size and position of tumor with central irregular areas of calcification.

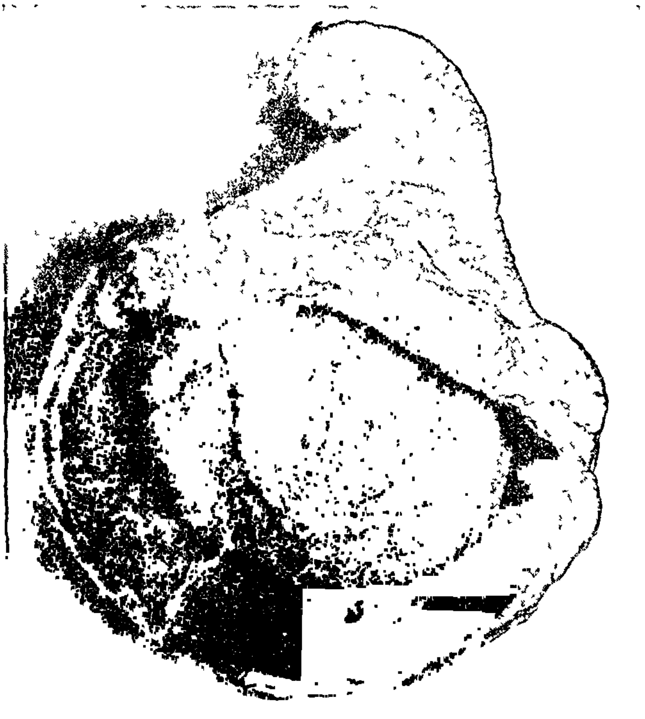

FIG. 2. Tumor, split longitudinally. Central mass is old blood.

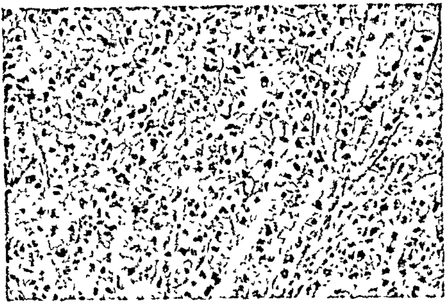

FIG. 3. Section of tumor showing large clear cells with small, dark-staining nuclei.

Flat films of the abdomen, followed by excretary urograms (fig. 1) showed the tumor occupying a position anterior and inferior to the right renal pelvis with an irregularly calcified central area. The right renal pelvis was apparently normal in shape, slightly larger than that on the left, and only the upper portion of the right ureter was visible. In upright views the tumor shadow could be distinguished from the lower border of the liver by the interposition of a gas-filled segment of colon. It was felt from the radiographic examinations that the tumor might be a large dermoid cyst.

Blood and urine analyses were unremarkable except for 15 white blood cells per high powered field, and a sedimentation rate of 14 mm/hr.

On her fourth hospital day the patient was operated on using open drop ether anesthesia. Upon opening the abdomen, a large retroperitoneal tumor was encountered which was intimately attached to the lower pole of the right kidney and in such close relation to the right renal pelvis as to make any attempt to separate it from what appeared to be normal kidney substance grossly impracticable. There were whitish, nodular areas on the surface of the tumor, and the entire mass seemed included in the capsule of the kidney. The tumor separated from the adjacent tissue with ease. The right kidney and the attached tumor mass were removed in one piece with very little difficulty. Following closure of the abdomen, the patient showed no adverse reaction to her surgery. Recovery was prompt, and the patient was dismissed from the hospital on her fifth post-operative day. Re-examination 6 weeks from that time showed only a well-healed wound and some increase in weight. There was no evidence of metastasis.

Following surgery the specimen was split longitudinally (fig. 2). There was a large cystic cavity with hemorrhagic material in the tumor which apparently had given calcific shadows on preoperative x-rays. Surrounding this was a rim of somewhat nodular, whitish material extending to and tending to widen the lower pole of the kidney. A capsule-like membrane was interposed between the tumor and grossly normal kidney substance.

Stained sections of the specimen (fig. 3) revealed atypical epithelial cells with abundant clear or pale granular cytoplasm, distinct cell borders, and deeply chromatic nuclei. In places they seemed to have an alveolar arrangement or glandular appearance. The pathological diagnosis was clear cell carcinoma of the kidney, or hypernephroma.

Re-examination of patient in May 1953 revealed no evidence of tumor spread or recurrence, normal growth and good nutritional state of the child. These findings make the prospect of permanent cure encouraging.

SUMMARY

A case of hypernephroma or clear cell carcinoma of the kidney occurring in a 7-year-old girl has been presented with illustrations. This is a tumor of extreme rarity in childhood, some authorities even doubting its existence prior to adult life. The patient was operated on and two years later presents encouraging prospects of permanent cure.

1700 Pine Grove Ave., Colorado Springs, Colo.

Addendum: Since preparation of this article for publication two other cases of hypernephroma in childhood have been published by Hempstead, R. H., et. al: Jour. Urol. **70**: 152, 1953.

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CLINICAL EXPERIENCE WITH THE SKEGGS-LEONARDS ARTIFICIAL KIDNEY

WALTER A. KEITZER, MANLEY L. FORD AND EDWARD W. MILLER

The purpose of this paper is to review our experience with the artificial kidney at the City Hospital of Akron during the past 2 years. Merrill[1-4] has contributed an excellent review on the subject and has recorded a large clinical experience with the Kolff kidney. Our experience has been with the more compact, more easily transportable, mechanically more simple Skeggs-Leonards artificial kidney (fig. 1). This kidney is capable of ultrafiltration. It has a comparable dialyzing area. Its volume is less than 500 cc. It is approximately the size of a bed-side stand. Its construction and assembly are sufficiently simple that the personnel of an average general hospital can be trained to assemble and apply it.

The stainless steel cabinet contains the two pumps and motors for the blood and dialyzing fluids, and the heating unit. The pumps will deliver up to 700 cc per minute without hemolysis. Dialyzing fluid flow may be altered by varying the diameter of the rubber tubing. Blood flow may be altered by varying the pump speed. The heating unit controlled by a DeKhotinsky thermostat maintains the desired dialyzing temperature.

The 18 by 12 inch rectangular dialyzer of 22,000 square centimeters dialyzing surface sets on top of the cabinet. Blood flows between sheets of cellophane. Dialyzing fluid flows in the opposite direction between the reverse side of the cellophane and the rubber mats.

Assembly of the kidney and its sterilization with live steam are performed by the surgical nurses. This requires from 2–3 hours. It may be set up hours or even days in advance, if the dialyzing unit is kept moist.

Following assembly, testing, sterilization and cooling or storage of the artificial kidney, the patient is brought to the operating room, usually in his own bed. Under local anesthesia, polyethylene catheters are inserted by way of the saphenous vein into the vena cava, and the homolateral antecubital vein into the subclavian vein, and kept open with 5 per cent glucose and distilled water. The blood side of the dialyzer is transfused with one unit of compatible heparinized blood. The patient is heparinized. The catheters from the patient are attached to the artificial kidney. The blood is taken from the leg vein, pumped into the bottom of the dialyzer, exits at the top through an air trap and returns to the patient through the arm vein at from 150 to 200 cc per minute. The dialyzing fluid is pumped from carboys through the dialyzer in the opposite direction at 400 to 600 cc per minute and is discarded (fig. 2).

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Unit built by Raymond W. Allen, designing engineer, Akron, Ohio

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chromatic nuclei. In places they seemed to have an alveolar arrangement or glandular appearance. The pathological diagnosis was clear cell carcinoma of the kidney, or hypernephroma.

Re-examination of patient in May 1953 revealed no evidence of tumor spread or recurrence, normal growth and good nutritional state of the child. These findings make the prospect of permanent cure encouraging.

SUMMARY

A case of hypernephroma or clear cell carcinoma of the kidney occurring in a 7-year-old girl has been presented with illustrations. This is a tumor of extreme rarity in childhood, some authorities even doubting its existence prior to adult life. The patient was operated on and two years later presents encouraging prospects of permanent cure.

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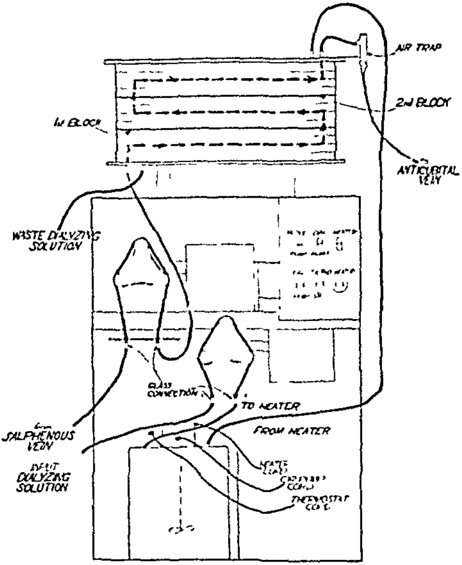

Fig. 2. Diagram showing circulation of blood and flow of dialyzing fluid in Skeggs-Leonards artificial kidney.

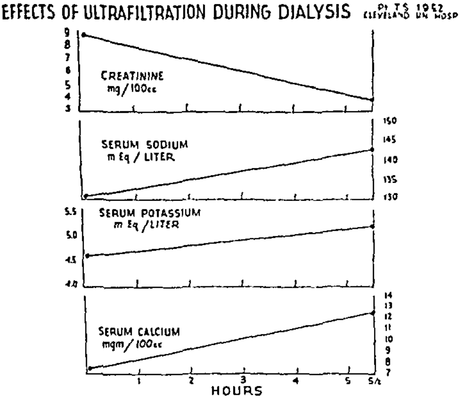

Fig. 3. Ultrafiltration and dialysis in patient with uremia and marked edema. (Patient T. S., University Hospital, Cleveland, Ohio. Courtesy of Dr. J. Leonards.)

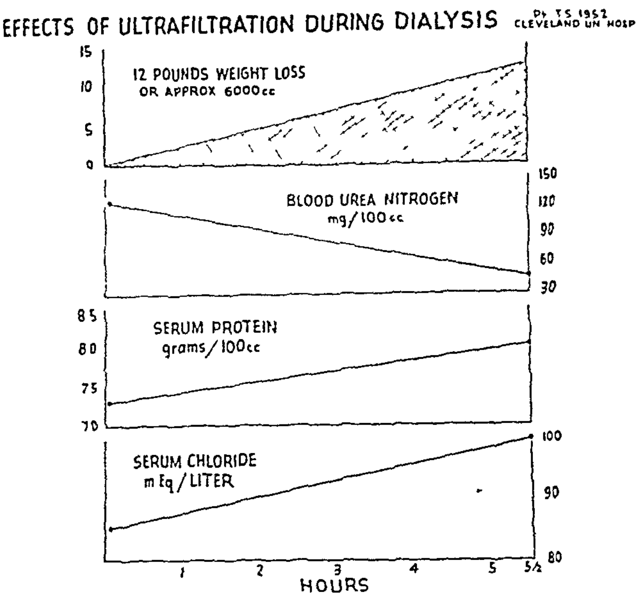

FIG 4. Continuation of figure 3

The indications for use of the artificial kidney have been outlined and discussed by several authors.[5-17] Its usefulness will vary with the knowledge and experience of those using it. Our experience has been purely clinical in an effort to determine whether the artificial kidney is a practical instrument in the therapy of uremia in a typical average general hospital. We have enjoyed technical advice from Dr. Leonards. We have no research grants. We have dialyzed patients with chronic uremia as a temporary measure and to develop our procedure, and patients with acute uremia to tide them over until their kidney function recovered.

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TABLE 1. *Clinical conditions in which the artificial kidney might benefit a patient*

I. Acute reversible uremia

A. Prerenal
  1. Protracted vomiting, i.e. intestinal obstruction.
  2. Severe diarrhea or fistula of small intestine. Infantile diarrhea.
  3. Eclampsia-toxemia pregnancy-abortion.
  4. Intestinal hemorrhage.
  5. Cardiac failure with acute uremia.
  6. Dehydration-heat stroke.
  7. Addisonian crisis.
  8. Diabetic acidosis with acute uremia.

B. Renal:
  1. Lower nephron nephrosis:
    a. Traumatic shock.
    b. Surgical shock.
    c. Transfusion anuria.
    d. Crush syndrome.
    e. Severe burns.
    f. Sulfa drug nephrosis.
    g. Acute glomerular nephritis.
    h. Acute poisonings:
      1) Bichloride of mercury
      2) Bromides
      3) Barbitals
      4) Carbon tetrachloride.
    i. Hepato-renal syndrome.

II. Chronic uremia

A. Prerenal:
  1. Azotemia of heart failure
  2. Chronic ulcerative colitis
  3. Malnutrition
  4. Intestinal obstruction chronic

B. Renal:
  1. Chronic glomerulonephritis
  2. Chronic pyelonephritis
  3. Malignant hypertension.

C. Postrenal:
  1. Nephrolithiasis, bilateral
  2. Bilateral hydronephrosis.
  3. Contraction bladder neck.
  4. Prostatic obstruction.

III. Nephrotic states (with or without uremia ultrafiltration)

A. Prerenal:
  1. Heart failure with anasarca
  2. Pulmonary edema
  3. Cerebral edema

B. Renal
  1. Nephrosis (chronic glomerular nephritis)
  2. Chronic pyelonephritis

IV. Electrolyte imbalance

A. Hyperkalemia
B. Hypernatremia
C. Hyponatremia
D. Preparation of poor risk for surgery.

In our brief experience of dialysis in 25 patients for a total of 32 applications, we are not in a position to give any specific indications or contra-indications. We can only suggest the possibilities and use the experiences of others to make an outline of the various conditions where dialysis might be of benefit (table 1).

It is our opinion that the urologist is peculiarly suited to handle the artificial kidney application by his familiarity with uremia by daily contact, by his ability to exclude obstructive uropathy, by his knowledge of fluid and electrolyte balance and by his ability to perform the necessitated minor surgical procedures.

Contra-indications for artificial kidney application are not well delineated. In view of the required heparinization, the threat or presence of active bleeding may constitute a hazard. Protamine sulfate, which is used following dialysis, will rapidly counteract the effect of heparinization. If the application is the

No.	Pt.	Age	Sex	Clinical Condition		BUN before	Hrs. Di.	BUN after	Clin. Resp.	Results & Findings at Autopsy if Done
Clinical application in acute uremia										
1	GO	39	F	Post partum eclampsia		105	0.1	77	Died	Died in convulsion on kidney
2	KF	50	F	Barbital & bromide suicide		95	2.0	66	Died	4 days later pneumonia
3	FB	34	F	Post partum hemorrhage		139	5.5	64	Good	Cured
4	LW	57	M	Crushing auto accident		130	6.0	60	Poor	Died-1 hr tear sup. mes. art.
5	WP	34	M	Post splenectomy shock		190	8.0	118	Good	Cured
6	VS	46	F	Traumatic shock		142	6.0	44	Good	Cured
7	GF	70	F	Postop. perforated ulcer		170	7.0	64	Fair	Died 24 hrs. peritonitis.
8	BB	28	F	Eclampsia, prem. sep. hemmor.		163	1.5	70	Died	Cardiac standstill potass.
9	DR	52	M	Spleno-reno-pancreo-colectomy		146	3.0	115	Poor	Died 6 days. Uremia
10	TB	2	M	Wilms tumor. Rt. nephrectomy	#1	110	2.0	78	Fair	Died 18th postnephrectomy
					#2	156	4.0	93	Good	Left renal infarction.
Clinical application in chronic uremia										
1	TW	48	M	Chronic nephritis, hypertension. Pulm. edema	#1	120	1.7	95	Good	Up & about; able to eat
					#2	150	3.0	95	Good	Again improved
				Coma, convulsions.	#3	140	3.0	121	Poor	Died two days later
2	EG	33	F	Postop renal failure	#1	156	4.0	54	Good	Cleared mentally
				Dehiscence & coma	#2	154	3.5	34	Fair	Died 3 days Chr. nephritis
3	IM	32	F	Malignant nephrosclerosis	#1	195	4.0	52	Good	Rt. adrenalectomy
				Uremic convulsions	#2	172	1.5	116	Fair	Died one week later. Convuls.
4	JW	32	M	Malignant hypertension		282	4.0	184	Poor	Died 1.5 hrs. after dialysis.
5	ZI	63	M	Postop. spleno-renal shunt		164	1.0	110	Poor	Died 24 hrs. Cirrhosis
6	LF	49	M	Malignant hypertension		154	4.0	76	Poor	Died shortly after dialysis.
7	BS	50	M	Malignant hypertension		152	4.0	110	Poor	Died 2 hrs. Pulm. infarction.
8	AM	45	F	Polycystic kidneys & convul.	#1	204	3.5	84	Good	Did well for 3.5 months.
					#2	200	4.0	106	Good	Died 17 days later.
9	WS	62	M	Arteriosclerosis & anasarca		—	0.3	—	Poor	Died in convulsion on kidney
10	FF	34	M	Rt. hydro.; lt. nephrostomy c calculus.	#1	137	5.5	33	Good	Improved for one week; uremia
				Bleeding ulcer	#2	234	2.0	156	Poor	Recur. Died 24 hrs.; convuls.
11	MM	55	F	Diabetes, pneumonia, coma		203	4.0	93	Fair	Died 48 hrs. Uremia & diabetes
12	LB	78	F	Heart fail. hepatitis, edema		114	4.5	71	Poor	Died 11 hrs. later
13	MW	43	M	Malignant nephrosclerosis		309	4.0	144	Good	Died 6 days later, uremia
14	RB	38	M	Staghorn in only lt. kidney Dialyzed preoperatively		175	4.0	63	Good	Living post-lithotomy but still uremic.
Clinical application in nephrotic patient										
1	JW	49	M	Chronic glomerular nephritis and anasarca. Convulsions		28	4.0	16	Good	Cured. Working daily

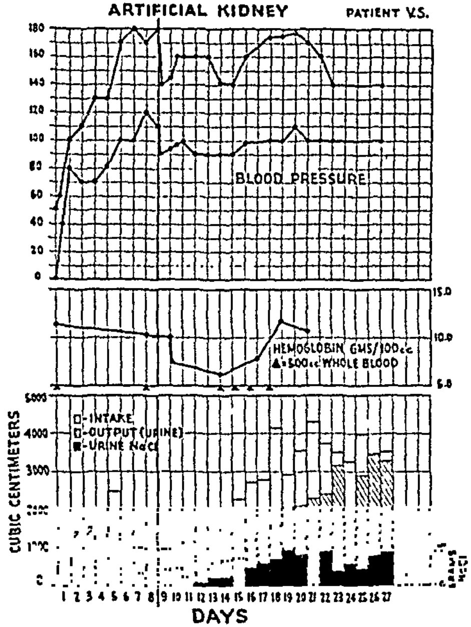

FIG. 5. Acute uremia showing response to dialysis. (Patient V. S., City Hospital of Akron.)

only chance to maintain life, it should not be withheld. Patients with malignant hypertension and uremia would not be expected to and do not respond well to dialysis. We have divided our clinical material into those with acute uremia, chronic uremia and those where ultrafiltration was thought to be an outstanding factor (table 2).

ACUTE UREMIA

Patients with acute uremia due to a reversible renal lesion not responding to conservative treatment are the ideal subjects for dialysis. Despite the extreme importance and application of conservative treatment by dietary, fluid and electrolyte balance management, there are patients in acute uremia who will die unless some type of dialysis is used. We believe that the artificial kidney is a practical means of salvaging many of these patients. Unfortunately, many of these patients are seen only after they are in extremis and die before, during, or shortly after application of the kidney. Education of the general profession in the use of proper conservative treatment of uremia and the importance of early consultation for dialysis will save more lives.

Example 1. V. S., a 46 year old white nurse, was anuric from shock incidental to multiple fractures sustained in an automobile accident. On her eighth post-

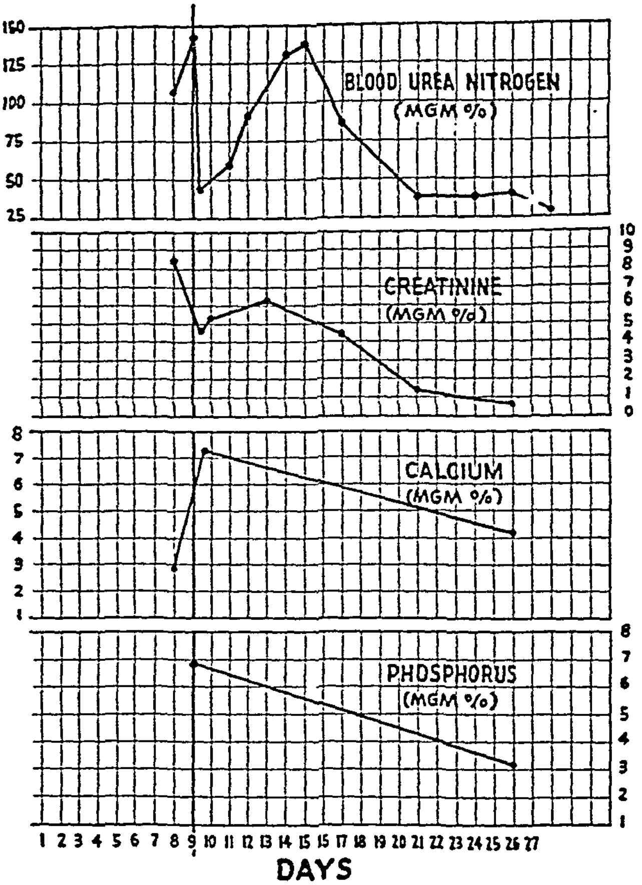

FIG. 6. Continuation of figure 5

accident and anuric day, she was comatose and convulsing. The abdomen was distended and there was fluid in the right chest. She was dialyzed for 6 hours (figs. 5, 6 and 7). The blood urea nitrogen dropped from 142 to 44 mg./100 cc. The CO_2 combining power rose from 17.6 to 22.5 mEq/L. The patient became mentally alert and the convulsions ceased. The blood pressure dropped from 200/100 to 140/90 mm. Hg. Diuresis occurred on the sixteenth day. She was discharged on her twenty-sixth day.

Since diuresis did not occur until the sixteenth day, it is our opinion that the artificial kidney was life saving in this instance.

Example 2. F. B., a 34 year old white woman with a history of pre-eclampsia, was anuric from shock and blood loss incidental to delivery. By her eighth postpartum day her condition appeared critical and the artificial kidney was used for 5½ hours. Clinical response was excellent. The blood urea nitrogen dropped from 139 to 64 mg./100 cc. Diuresis occurred the following day. The patient recovered rapidly and was discharged on the twenty-second hospital day. Very probably the patient would have recovered without dialysis. Her convalescence was probably shortened. It is impossible to foresee the time of diuresis, and it is probably wiser to administer the artificial kidney early in critical cases.

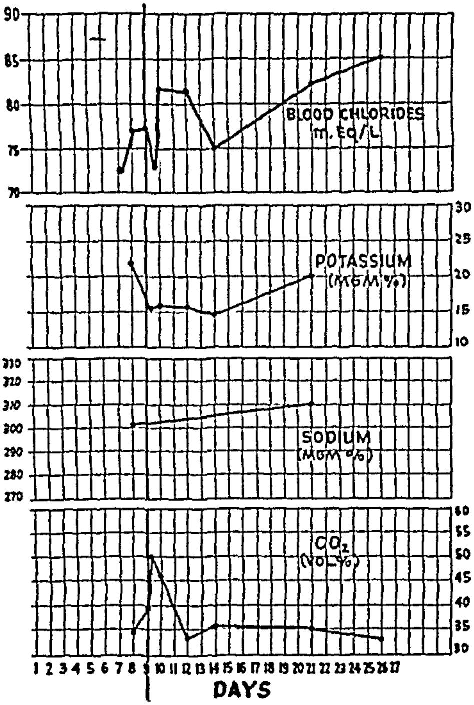

FIG. 7. Continuation of figure 5

CHRONIC UREMIA

The patients with chronic uremia were hopelessly ill; all are now dead. A few patients' lives were prolonged. Valuable experience was gained. It became clinically apparent that a patient too long in severe uremia would not survive, no matter how long dialysis might be instituted.

Example 1. A. M., a 45 year old white woman, had been treated for polycystic kidney disease for 5 years. She was admitted in uremic coma, was markedly distended and anemic. She was dialyzed for 3½ hours. The blood urea nitrogen dropped from 204 to 84 mg./100 cc. The CO_2 combining power rose from 11.2 to 15.3 mEq/L. The chlorides rose from 68 to 80.0 mEq/L. Marked clinical improvement followed, urine output increased; the patient became mentally alert, vomiting ceased, and she was able to eat. Three months later uremia recurred and she was again dialyzed for 4 hours. The blood urea nitrogen dropped from 200 to 108 mg./100 cc. Her clinical condition again improved, but uremia gradually recurred and she died 17 days after her second dialysis.

Example 2. E. G., a 33 year old white woman, had anuria following a transfusion incidental to a pelvic laparotomy. She was comatose, convulsing and emaciated. Her abdomen was distended. On the seventh day of anuria she was dialyzed for four hours. The blood urea nitrogen dropped from 156 to 54 mg./100 cc. Convulsions ceased. She became mentally alert. Six days later she again became semicomatose and was dialyzed for 3 hours. The blood urea nitrogen was reduced from 154 to 34 mg./100 cc. The day following the second dialysis she suddenly died. Autopsy showed far advanced chronic glomerular nephritis, cardiac hypertrophy, diffuse hemorrhages of the arachnoid, hemorrhagic lobular pneumonia, pulmonary edema, atalectasis and emphysema.

It was impossible to determine beforehand that this patient was a chronic uremic rather than an acute uremic, as expected.

ULTRAFILTRATION

Example 1. J. W., a 49 year old white man, was admitted with complaint of marked swelling of the legs and abdomen and generalized edema progressively developing over 5 months. He had been treated with mercurials, salt restriction and diet by his physicians. Examination disclosed an edematous facies. There was anasarca involving even the chest wall. Scattered rales were present through the lung fields. There was intra-abdominal fluid. The urine showed a 3 plus albumin, 1.018 specific gravity, a few white blood cells and red blood cells and granular casts. The blood urea nitrogen was 16 mg./100 cc. Potassium was 4 mEq/L, chlorides 72.2 mEq/L, total plasma proteins 3.17 gm./100 cc, albumin 1.7 gm./100 cc, urea clearance 83 per cent of normal. Transfusions, antibiotics, ammonium chloride and concentrated albumin were given over a period of 1 week without benefit. ACTH was given in ten-day course. On the ninth hospital day general convulsions developed. Fluid, 1500 cc, was removed by abdominal paracentesis. Convulsions continued; the outlook appeared fatal; the blood urea nitrogen was 28 mg./100 cc. The patient was placed on the artificial kidney for 4 hours. At the end of the procedure the patient was mentally alert, convulsions had ceased and he appeared clinically improved. With no therapy other than antibiotics he continued to improve and was discharged on the twenty-sixth hospital day. He has remained well.

Possibly, reduction by ultrafiltration of the brain edema stopped the convulsions. Why he went on to recover from his nephrotic state is unknown.

SUMMARY

The clinical application in an average general hospital of the Skeggs-Leonards artificial kidney has been described.

It has been indicated that the Skeggs-Leonards kidney will not only effectively dialyze nitrogen excess in the blood and correct electrolyte imbalance, but will also ultrafiltrate if desired.

Clinical conditions where the artificial kidney might be of benefit are outlined and classified into four basic groups.

Our clinical experience with 25 patients, upon whom a total of 32 dialyses have been performed, are tabulated. Illustrative cases in the various groups have been summarized.

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RECOVERY FROM RENAL ISCHEMIA IN RATS AND DOGS

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The desirability of employing vividialysis or exsanguination-transfusion for the treatment of uremia due to acute renal insufficiency is still under debate.[1, 2] Even those favorably inclined towards employment of dialysis agree that spontaneous recovery may be anticipated in most patients free from complications who are conservatively and properly handled.[3, 4]

Proponents of the use of the "artificial kidney" or intestinal or peritoneal lavage, and those who have reviewed the results of such therapy, have been loath to assert that use of such methods determines the outcome in any case. In 1949 Snapper wrote, ". . . no certain conclusions can be reached as to whether dialysis by the artificial kidney is actually a life-saving device."[5] Kolff, in 1950, wrote, "I do not and never did claim that I ever saved a patient with the artificial kidney, although many of my patients have now recovered from severe uremia."[6] More recently, Merrill has argued that use of the artificial kidney can relieve hyperkalemic intoxication, facilitate employment of conservative management, help mobilize patients and produce symptomatic improvement, and that it is therefore pointless from the clinical point of view to argue whether dialysis changes the mortality.[7, 8] While acutely anuric Korean battle casualties treated with the artificial kidney appear to have a lower mortality than others conservatively managed,[9] the question still remains whether kidneys damaged so severely as to remain anuric or oliguric to the patient's demise, even with the best conservative therapy, have the potentiality for eventual recovery to a degree of function compatible with prolonged life.

The variability of the clinical syndrome makes it difficult to answer confidently from experience with human subjects.[4, 5, 10] Myers has surveyed the literature reporting individuals with complete anuria of from 20 to 60 days, some with survival.[11] The average duration of oliguria in acute renal failure is about 10 to 12 days, varying in most cases from a few days to 3 weeks.[4] The difficulty of answering the question posed on the basis of clinical material is clear. Commenting on cases of prolonged oliguria or anuria which survived with conservative therapy,

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* W. K. K tment of Physiology, F

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Swann and Merrill found all reviewed to have been chronically ill at the onset of oliguria, and hence catabolizing relatively small amounts of fat and protein.[4] It must be added that survival to the time of diuresis may still be followed by death due to renal failure.[4]

A simple approach to the problem of renal repair after acute injury is possible in animals and has been used, but the importance of the reported results does not seem to have been widely appreciated. Koletsky and Dillon have reported that ischemic damage of the kidney, uniformly fatal within a few days, may with time be repaired sufficiently to maintain life.[12] Our results confirm and extend their findings. Since ischemic renal damage seems prominent in various clinical circumstances[13, 14] these animal results may have bearing on the situation obtaining in human beings.

METHODS

Male rats of the Sprague-Dawley strain weighing 200 to 300 gm. were used. The left renal artery was occluded with a rubber-tipped serrefine clamp for 2 hours. In control animals right nephrectomy was performed immediately after removing the clamp. In test animals right nephrectomy was delayed for 21 days. Blood was obtained at sacrifice through cardiac puncture.

In mongrel dogs the left renal artery was occluded for 6 hours with 2 serrafines with rubber-covered tips. In 2 control dogs the right kidney was removed at the same operation while in 8 test dogs nephrectomy was delayed several weeks. At each initial operation the presence of left multiple renal arteries was excluded and this later confirmed by necropsy. Blood pressures were determined with a mercury manometer by direct femoral arterial puncture. Plasma urea nitrogen determinations (PUN) were made with urease digestion and a direct nesslerization procedure on Somogyi filtrates.

RESULTS

Rats. All 8 control rats (nephrectomy at time of clamping) died, 2 in 24–48 hours, 5 in 48–72 hours and 1 in 72–96 hours after operation. All of 13 test rats (clamping without immediate nephrectomy) lived to have right nephrectomy performed 21 days later. Of these, 1 died 24–48 hours, one 72–96 hours and one 120–144 hours after nephrectomy. Ten of the 13 survived to sacrifice 33 to 48 days after nephrectomy.

Table 1 shows the weights of the rats and their kidneys and the PUN levels at sacrifice. The concurrently determined PUN levels of 2 normal rats similarly sacrificed were 15.7 and 11.8 mg. per cent. The right kidneys of the test rats were hypertrophied, and were largest in those dying within 6 days after nephrectomy, i.e., where left kidney function had failed. These rats also showed marked atrophy of the left kidney. At sacrifice the left kidneys of the 10 test rats surviving right nephrectomy 33 days or longer averaged almost as large as the obviously hypertrophied companion right, demonstrating that hypertrophy of the pre-

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TABLE 1

Body and kidney weights and PUN levels of rats having 2 hour left renal arterial occlusion and right nephrectomy 21 days later, and of controls

Orig BW* (Gm)	Nephrex BW† (Gm)	Final BW‡ (Gm)	Survival§ (days)	RKW‖ (mg %)	LKW** (mg %)	PUN†† (mg %)
			Test survivors			
212	260	211	47	685	645	139
234	268	328	41	578	538	21
262	298	212	48	622	—	83
246	287	314	33	523	491	32
210	253	270	43	561	463	21
202	236	298	41	574	495	29
230	291	340	43	591	478	32
238	255	229	33	596	585	46
264	278	247	33	588	500	79
264	280	264	33	509	481	69
Av 236	271	271		583	520	
			Test nonsurvivors			
222	250		4	740	162	
240	275		6	660	222	
282	301		2	605	163	
Av 248	275			668	182	
			Controls			
260				392		
272				417		
270				526		
260				410		
270				463		
220				486		
225				427		
227				509		
Av 251				454		

* Body weight at left arterial occlusion

† Body weight at right nephrectomy

‡ Body weight at sacrifice

§ Time from nephrectomy to death or sacrifice

‖ Right kidney weight at nephrectomy in mg per 100 gm of body weight at nephrectomy

** Left kidney weight at sacrifice or death in mg per 100 gm of body weight at sacrifice for survivors or per 100 gm of body weight at nephrectomy for nonsurvivors

†† Plasma urea nitrogen at sacrifice in mg per 100 ml

viously ischemic left kidney followed right nephrectomy. Elevated PUN levels were present in all except perhaps 2 of the survivors. All left kidneys of the test group showed grossly abnormal morphology in some respect, as pitted surfaces, yellow-tan color, asymmetrical shapes, scarring, etc. The gross and microscopic anatomy of such kidneys has been described elsewhere.[12]

Dogs. Both of the 2 dogs nephrectomized at the first operation died within 8 days. Of the other 8 animals, 6 nephrectomized 24 to 46 days after left renal arterial occlusion died 4 to 18 days after nephrectomy with elevated PUN. A seventh died as a result of intravenous urokon injection before right nephrectomy. X-ray visualizations 21 and 42 days after arterial clamping showed the left kidney to be small, but irrigated with blood and excreting urokon. Except for being small the left kidney had the gross and microscopic picture of a well functioning kidney.

One dog survived right nephrectomy performed 51 days after left renal arterial occlusion and was sacrificed 45 days thereafter in apparent good health. X-ray pictures taken 4 days before nephrectomy revealed a left kidney smaller than the right, with both excreting urokon. Para-aminohippurate and inulin clearances fell from prenephrectomy values of 75 and 20 cc per minute to 30 and 6.5 four days after nephrectomy and rose to 49 and 13.5 just before sacrifice. PUN, which had risen after nephrectomy to a high of 48 milligrams per cent, fell to 22 while weight remained unaltered, and blood pressure remained normal. On the forty-fifth day after nephrectomy the abdomen was opened and the kidney examined. A single left renal artery was pulsating and no prominent ureteral artery, prominent capsular vessels or adhesions were found. The kidney looked normal and weighed 20 gm. as compared with 27 gm. for the previously removed right kidney. Some focal scarring and mild focal dilatation of Bowman's capsule were seen on microscopic examination.

DISCUSSION

The results show that while a rat kidney immediately after renal arterial occlusion for 2 hours is unable to maintain life, it becomes able to do so when allowed 21 days to recuperate. Given time, the kidney in these circumstances manifests considerable repair, and this conclusion is strengthened by the demonstration that the functional residuum of even 2 kidneys remaining after 2 hour bilateral arterial and venous occlusion does not prevent uremic death.[15] In the 3 animals failing to survive delayed nephrectomy the left kidney weights were much the smallest of the series, indicating either that injury had been more severe than in the others or that the potentiality for hypertrophy had been low. These results are in agreement with those of Koletsky and coworkers.[12, 15]

Our 2 control dogs with immediate right nephrectomy died within a few days as did the 2 similar dogs of Hamilton et al.[16] Of the 6 test dogs dying after nephrectomy, 1 lived 18 days. This is probably a lengthened survival as compared with the results of Hamilton et al. for dogs with one kidney similarly injured and immediate removal of the other, and those of Block et al. for 4 to 6 hour bilateral renal arterial occlusion.[14]

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We cannot predict whether the animal dying after urokon injection would have survived nephrectomy, since we have seen death occur in uremia even during polyuria.

The animal surviving to sacrifice on the forty-fifth day appears to show the beneficial effects of allowing time for repair. With only 10 control dogs (2 of Hamilton et al., 6 of Block et al., with bilateral 4 to 6 hour occlusion, and 2 of ours) showing 100 per cent mortality, and 6 additional with 4 hour occlusions showing 50 per cent mortality,[16] it cannot be stated with certainty that all dogs will die following renal arterial occlusion for 6 hours with concurrent contralateral nephrectomy, although this seems highly probable. It appears that dogs, like rats, can recover from acute otherwise fatal ischemic renal injury.

Generalization as to other types of acute renal injury and other species is not warranted. While, as indicated, the answer to the question posed is not easily derived from clinical material, rare reports such as that by Hamburger et al.[17] lead similarly to the conclusion that repair adequate for survival may occur if life is prolonged by removal of toxins.

SUMMARY

Rats subjected to 2 hour unilateral renal arterial occlusion and concurrent contralateral nephrectomy die within a few days.

The great majority of rats with 2 hour renal arterial occlusion in which contralateral nephrectomy is delayed for 21 days survive for a long period of time, often with residual renal damage.

In 2 dogs reported here and 2 elsewhere 6 hour unilateral renal arterial occlusion together with concurrent contralateral nephrectomy was followed by death within 10 days. In 6 additional dogs with 4 to 6 hour bilateral occlusion, all were reported elsewhere to have died within several days.

Of 7 dogs with 6 hour unilateral renal arterial occlusion in which contralateral nephrectomy was delayed for several weeks, 1 survived nephrectomy 18 days and another survived to sacrifice 45 days later.

The results indicate clearly in rats and probably in dogs that a degree of renal ischemic injury severe enough to be fatal in an animal depending upon this single injured organ, may with time be repaired sufficiently to allow the kidney to maintain life.

We wish to thank Dr. Carlos Restrepo Acevado and Dr. John C. Sutherland for having examined the tissue sections.

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MANIPULATION OF URETERAL CALCULI: MEATOTOMY AND IMMEDIATE DELIVERY

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The manipulative removal of ureteral calculi is one of the most interesting phases of urologic practice. Much ingenuity has been expended in the invention of instruments for this work and urologists are all familiar with the great variety of these available.

The procedure which is the subject of this paper is not in itself a new one; however, its application in this manner has not been advocated in the literature nor, so far as I know, regularly used. This procedure is that of immediate cystoscopic incision of the ureteral meatus and intramural ureter when an engaged stone becomes halted at the ureterovesical junction or just above. This is the site at which stones which have been captured by various instruments usually become impacted.

In such situations the common practice has been the application of constant traction. Intermittent traction at intervals of a few hours is probably next in popularity. Those who use wire baskets have advocated dilatation of the intramural ureter by expanding the basket at this point. Rubber balloons (Dourmashkin bags) have served the same purpose.

Ureteral meatotomy has often been done in the past as a means of facilitating spontaneous passage of stones and occasionally as a preliminary to further instrumentation. This last procedure has a disadvantage in that any large incision makes it more difficult to exactly identify the true channel and thus to pass other ureteral instruments.

When stones have become spontaneously impacted in the intramural ureter it is an old practice to do meatotomy or incision directly on the stone. Recently, resection through the wall of the ureter with the McCarthy resection instrument has been advocated as a means of freeing these stones (Davis et al.). In this circumstance we have always preferred using the Collings cystoscopic blade electrode, cutting the ureter from inside out. An extension of this practice led to the presently described procedure.

In recent years we have made it a practice to use the loop catheter in manipulation of stones although occasionally the basket is likewise used. When the stone is engaged, if it is a small one, it usually comes through the orifice with comparatively little tension. The larger ones usually become impacted just above or in the intramural ureter. Instead of applying either immediate heavy pull or continuous traction we have made a practice of cleanly cutting the ureteral meatus and intramural ureter with the high frequency current.

This is easily done by the following procedure: The loop catheter or basket is held under light tension by an assistant so that the stone will not escape or fall

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back. The cystoscope (a McCarthy instrument with a beakless sheath) is then easily removed, leaving the loop catheter in place. The cystoscopic sheath is immediately re-inserted next to the catheter. This easily accomplished with the 8 mm. (24F) sheath in both men and women. The meatotomy is done with the Collings cystoscopic knife with an offset blade, which fits through the McCarthy routine cystoscope with ease. The blade is put inside the ureteral orifice alongside the loop of the catheter (or the wires of the basket). It is almost like doing a episiotomy with the head bulging on the perineum. The small spurting arteriole which usually appears is easily coagulated with the blade. Slight tension is maintained by the assistant throughout the procedure. The operator can put on a heavier pull at any time. The loop or basket is thus delivered into the bladder.

In the aftercare we feel that it is more important to keep the bladder deflated rather than the renal pelvis, and so instead of a ureteral catheter, a small Foley catheter is left in the bladder from 24 to 72 hours depending upon the extent of the incision.

We think that it is better to make a clean incision of controlled extent and depth than to tear or dilate an opening of similar size. The parallel case of episiotomy and its advantages comes to mind. Cutting from inside out rather than outside in has an advantage in that the stone is sometimes freed without carrying the incision all the way through into the bladder.

This procedure has been used to date in 13 cases without any deleterious side effect. It has not always been successful. In two cases the loop slipped off of the stone while incision was being made and it was not possible to re-insert the loop at the same sitting.

SUMMARY

In manipulative removal of ureteral calculi, when a captured stone becomes halted at the intramural portion of the ureter, we believe incision is preferable to either immediate heavy traction or continuous traction as a means of delivering the stone into the bladder.

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INTERSTITIAL CYSTITIS: A CAUSE OF PERSISTENT BLADDER DISABILITY

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The postoperative course of patients who have had transurethral resection of the prostate gland is occasionally complicated by the persistence of an irritable bladder. The usual cause for the irritable bladder can be found in an incomplete resection of the prostatic tissues, a necrotic residue of prostatic tissues, a persistent infection which delays epithelialization, strictures of the prostatic fossa or anterior urethra, or infection of the pelvic adnexa. A group of patients who failed to respond as expected following treatment of their prostatic lesions is presented. No usual cause of persistent symptoms was present. Interstitial cystitis, unrelated to the surgery, was found to be the cause.

Interstitial cystitis is relatively uncommon in the male. Authorities claim that interstitial cystitis occurs four to six times more often in the female than in the male. We believe this impression is an understatement. The seven male patients to be presented had interstitial cystitis. They had been diagnosed and treated for other genito-urinary disease. Failure to improve as expected led to further urological investigation. The diagnosis of interstitial cystitis was established by cystoscopy in each of these patients.

Interstitial cystitis is a chronic inflammation of the bladder which is identified pathologically by involvement of the bladder mucosa, the submucosa, and the muscularis. Panmural cystitis is a descriptive synonym. The bladder involvement is patchy in distribution. The involved areas lose their distensibility and linear cracking occurs when the bladder is overdistended. The etiology is unknown.

Interstitial cystitis is characterized clinically by day and night frequency of urination, marked urgency, and severe pain when the bladder is distended. The patient may point to a painful suprapubic spot which corresponds to the site of the bladder ulcer. The capacity of the bladder is decreased. The pain is due to edema and leukocystic infiltration within and about the nerve sheaths of the bladder. Examination of the urine is negative with the possible exception of microscopic hematuria. Cystoscopy reveals isolated, sharply demarcated, red areas on the bladder mucosa. Overdistention of the bladder causes linear, bleeding ulcers in the involved areas. This lesion has a predilection for the dome of the bladder. Noninvolved portions of the bladder are entirely normal.

Secondary interstitial cystitis is not to be confused with primary interstitial cystitis which is described above. Secondary interstitial cystitis is the end result of long-standing pyogenic infection of the bladder and has no place in this discussion.

CASE REPORTS

Case 1. T. G., aged 59, complained of frequency every one to two hours, nocturia of 10 times, poor urinary stream, and straining to void. General physical

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examination was normal. The prostate gland was small, benign, and symmetrical. Urinalysis was entirely normal. Catheterization showed no residual urine. Observation cystoscopy revealed an apparently normal bladder. The bladder neck was obstructed by a broad prostatic bar. Transurethral resection of the bladder neck was performed. Histological examination of the resected tissues showed chronic inflammation of the prostate gland. The patient failed to notice any amelioration of his symptoms. An upper urinary tract study was normal. A second resection was performed four months later. All manner of therapy was ineffective. Cystoscopy was performed using general anesthesia. Overdistention of the bladder caused bleeding. A typical area of interstitial cystitis with a bleeding linear ulcer was found in the area of the air bubble. Therapy directed toward the relief of interstitial cystitis has resulted in marked improvement. He continues to have nocturia two to three times and frequency every 4 hours.

Case 2. J. K., aged 41, gave a past history of much treatment without relief of his symptoms. He complained of frequency every two to three hours, nocturia three to four times, and suprapubic discomfort. General physical examination was normal. Urinalysis was normal. Rectal examination revealed a small prostate gland with induration of the right prostatic lobe. No residual urine was found on catheterization. Cystoscopy revealed a fibrous median prostatic bar. Transurethral resection of the prostatic bar was performed. The tissues were reported as chronic inflammation of the prostate gland. No improvement of any symptoms was admitted after complete healing. A second revision of the bladder neck was performed six months later. A small amount of sclerotic prostatic tissue was resected. The tissues were benign. The symptoms persisted. Subsequent cystoscopy using general anesthesia revealed a normal, healed bladder outlet. Overdistention of the bladder caused a linear, bleeding ulcer in the dome of the bladder. Therapy for the relief of the symptoms of interstitial cystitis has caused marked improvement in his symptoms.

Case 3. V. J., aged 61, complained of urgency, remarkable frequency and nocturia, and hematuria. A fourth resection of his bladder neck had been performed. His symptoms seemed to become more aggravated after each surgical procedure. General physical examination was normal. Rectal examination revealed a flat prostatic bed. The urine was moderately infected due to his recent surgery. The patient was hospitalized and cystoscopy was performed using general anesthesia. The bladder neck seemed adequately resected. The region of the air bubble and the left lateral wall of the bladder showed multiple areas of interstitial cystitis with linear ulcerations. These areas were fulgurated. The maximum bladder capacity under general anesthesia was 5 ounces. Marked improvement in the severity of his symptoms was noted. Local therapy has been continued in the office.

Case 4. N. B., aged 69, was admitted to the hospital in acute urinary retention. His past history included frequency, nocturia, and urgency. General physical examination was normal. The prostate gland was flat and benign on palpation. A fibrous median prostatic bar was resected. The tissues were benign on histological examination. The postoperative course was uneventful. Marked bladder irritability persisted after healing was complete. He was readmitted to the hospital for cystoscopy under general anesthesia one year after surgery. The bladder was distended to 9 ounces. Multiple linear ulcers were noted to the right of the air bubble. The bladder neck was well resected and well healed. Office therapy was directed toward the relief of the interstitial cystitis. The patient has admitted much improvement in his bladder symptoms.

Case 5. H. S., aged 56, underwent cystoscopy after much conservative therapy for chronic prostatitis and seminal vesiculitis had failed to relieve his symptoms. Residual urine had never been found: Cystoscopy revealed interstitial cystitis and also the presence of a prostatic bar. The bladder was overdistended and the ulcers were fulgurated. A transurethral resection of the prostatic bar was done 6 months later. The patient has continued office treatments. He has never been entirely comfortable for any appreciable interval. Treatment is directed toward the interstitial cystitis when the symptoms seem to stem from that source. Stripping of the seminal vesicles and gentle massage of the prostatic bed offer relief of symptoms caused by the chronically infected adnexa.

Case 6. S. R., aged 52, was admitted to the hospital complaining of nocturia 20 times and frequency every hour. A bladder calculus had been removed 25 years ago. Physical examination was essentially normal. Rectal examination revealed a small, benign prostate gland. Two ounces of residual urine were found on catheterization. The urine contained a few pus cells. Cystoscopic examination revealed a prostatic bar. Bladder capacity was only fair. A transurethral resection of the prostatic bar was accomplished. A second resection was performed 10 months later but his symptoms were not improved appreciably. Within a month of the last resection, a cystoscopy was performed using general anesthesia. The bladder was forcibly distended to 10 ounces. An area of interstitial cystitis was noted on the left lateral wall of the bladder. His symptoms were improved but overdistention and fulguration of the ulcer were necessary two months later. He has remained well controlled with the benefit of office therapy.

Case 7. J. M., aged 64, received office treatment for many years for urethral strictures. The strictures were under excellent control and the patient was seen at infrequent intervals. Cystoscopy was performed when the patient complained of frequency, nocturia, and suprapubic pain. A median prostatic bar was found. Overdistention of the bladder caused much pain. Cystoscopy was repeated using general anesthesia. Overdistention at this time revealed an area of interstitial cystitis on the left lateral wall of the bladder. Office therapy directed toward the interstitial cystitis has effected marked relief. The prostatic bar has not been resected.

Each of the patients was in the prostatic age group. One patient had acute urinary retention. No remarkable amount of residual urine was found in the remaining 6 patients. The patients' bladders were irritable. They had frequency, nocturia, urgency, and pain. Cystoscopy revealed the bladder neck lesions, and surgical approach was accomplished in six of the seven patients. One patient was originally treated elsewhere and the original prostatic gland lesion was not observed. All resected tissues were benign. The histological descriptions emphasized the infected, sclerotic prostatic gland tissues.

A review of the clinical courses of these patients reveals the following pertinent fact The patients complained of irritable bladders Their symptoms were compatible with the diagnosis of fibrous prostatic gland sclerosis at the bladder neck We believe the interstitial cystitis was present at the initial examination but it was overlooked when the very apparent bladder neck disease was found Some of these patients had multiple operations before the less obvious cause of their disability was found

Healing of the prostatic fossa following transurethral resection of the prostate gland is completely accomplished within three months At this interval the patient should be comfortable Persistence of bladder symptoms following the healing of an adequately resected bladder neck may be caused by other entirely unrelated pathological lesions

The fibrous median prostatic bar and interstitial cystitis are sclerotic lesions in character There is no evidence that they are due to the same etiological agent

SUMMARY

The clinical histories and findings of seven male patients are presented Debilitating urinary symptoms persisted following prostatic therapy Marked improvement was effected after interstitial cystitis was found and treated

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brown black pigment were present in the superficial mucosa and were undoubtedly responsible for the "hair" like appearance seen grossly The pigment was fine, granular, and largely free in the superficial tissues rather than within cells Treatment of the slide with Weigert's borax—potassium ferricyanide differentiating fluid resulted in dissolution of 75 per cent of the pigment, all the smaller particles Diagnosis Pigmentation of the bladder, probably silver, chronic cystitis, resembling cystitis glandularis, focal epidermalization of the bladder mucosa

DISCUSSION

None of the standard American textbooks of Urology mention the entity or cystoscopic picture of argyrosis of the bladder Some textbooks on pathology briefly describe the deposit of silver in the bladder in generalized argyrosis Gettler[1] reported the most severe case of generalized argyria ever recorded and beautifully described the fate of silver in the human body In his case, the bladder epithelium contained no silver, the pigment was present in the submucosa, the connective tissue between muscle fibers, around blood vessels and within phagocytes

In a survey of the literature, the only mention of localized argyria of the bladder was a brief discussion by Priv Doz Dr V Blum of a case in which carcinoma of the bladder was attributed to the argyria[2]

Dr F K Mostofi stated that there were no cases of localized argyrosis of the urinary bladder on file at the Armed Forces Institute of Pathology [3]

With the widespread use of silver preparations in the bladder, we feel sure that this condition has been seen many times and not reported We believe the stubble-like appearance of the bladder mucosa is a unique, diagnostic cystoscopic picture The pigment was deposited in clumps within the superficial epithelium, between the cells, this differs from generalized argyria in which pigment is usually not present in the bladder epithelium It is not known whether the silver pigment contributed to the patient's symptoms Resection is offered as a method of treatment

SUMMARY

A case of localized argyrosis of the urinary bladder including cystoscopic and pathological features is presented

A review of the literature revealed no previous description of the cystoscopic picture

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THE DISADVANTAGES OF THE ELECTRORESECTOSCOPE FOR BLADDER TUMOR BIOPSY

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A large proportion of bladder tumor biopsy specimens removed with the electroresectoscope are unfit for detailed microscopic study because of the destructive effects of the electric cutting current.

The grading of bladder tumors may be difficult under the best of conditions. Nevertheless, accurate tumor diagnosis is a necessity if the patient is to be offered the best chance for cure. In classifying these tumors for the Bladder Tumor Registry of the American Urological Association at the Armed Forces Institute of Pathology every effort is made to study each specimen according to the following microscopic criteria: 1) cellular structure, that is, the type cell comprising the tumor, its degree of differentiation, and the relative frequency of mitotic figures; 2) the arrangement of the tumor cells, whether in separate papillary structures or in sheets; 3) the presence or absence of invasion of the bladder musculature.

Recent study of 100 consecutive bladder tumor biopsies referred to the Registry shows that most of the specimens were removed by the electroresectoscope. More than one-fourth of these were so extensively damaged by the electric current that accurate microscopic diagnosis was impossible (table 1).

The passage of the electric current through tissue causes considerable distortion of the surrounding structures. The cell nuclei become pyknotic and the entire cell, nucleus included, is elongated. The cell boundaries are lost; no mitoses are visible, and even such easily recognized structures as glandular or acinar formations may be disguised. These changes occur both in neoplastic areas and in normal tissue, with the result that the pathologist is unable to distinguish between the two (fig. 1, *A* and *C*).

The heat affects the tissue to a depth approximating from one to two high power fields of the microscope. Thus in the case of large papillary tumors, it may still be possible to make a correct diagnosis; but when the papillary tumor is small, single, and delicate, its entire thickness may be distorted. It is important also to realize that when the cutting current passes through the pedicle or stalk of a papillary growth, any tumor cells which may be infiltrating this structure or invading the bladder wall are likely to be altered beyond recognition. The

TABLE 1. *Comparison of biopsies obtained by electroresection and cold resection. Total cases, 100*

	CASES IN WHICH DISTORTION OF CELLS PRECLUDED DIAGNOSIS	
	Number	Per cent
Electrosection, 74 cases	21	30
Cold resection, 26 cases.	3	12

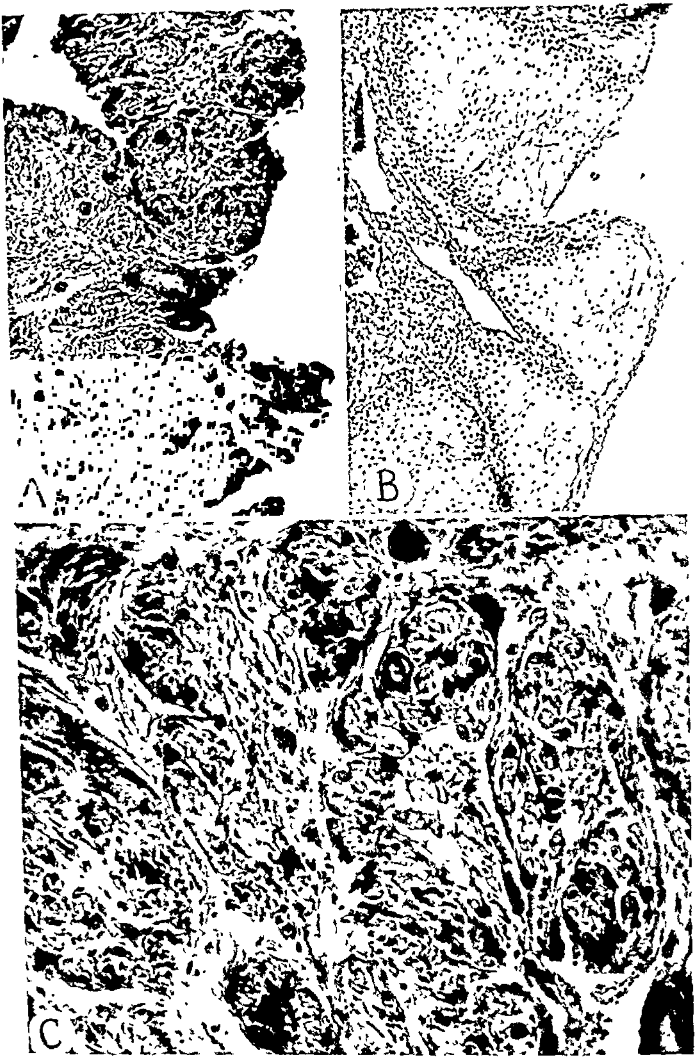

Fig 1 *A*, low power photomicrograph of segment of non neoplastic bladder tissue obtained with electrocautery. This biopsy strikingly resembles an infiltrating neoplasm. AFIP Accession No 267301-2 *B*, photomicrograph of an area in lesion reproduced in *A* not distorted by cautery effects. Cystitis and squamous metaplasia of bladder epithelium are clearly visible. *C*, higher power of an area of cautery distortion in same lesion. Even at this magnification the lesion appears malignant.

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THE DISADVANTAGES OF THE ELECTRORESECTOSCOPE FOR BLADDER TUMOR BIOPSY

ARCHIE L. DEAN, JR. AND J. E. ASH

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A large proportion of bladder tumor biopsy specimens removed with the electroresectoscope are unfit for detailed microscopic study because of the destructive effects of the electric cutting current.

The grading of bladder tumors may be difficult under the best of conditions. Nevertheless, accurate tumor diagnosis is a necessity if the patient is to be offered the best chance for cure. In classifying these tumors for the Bladder Tumor Registry of the American Urological Association at the Armed Forces Institute of Pathology every effort is made to study each specimen according to the following microscopic criteria: 1) cellular structure, that is, the type cell comprising the tumor, its degree of differentiation, and the relative frequency of mitotic figures; 2) the arrangement of the tumor cells, whether in separate papillary structures or in sheets; 3) the presence or absence of invasion of the bladder musculature.

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SUMMARY

The resectoscope appears to be a highly popular instrument for removing specimens of bladder tumors for microscopic examination. In a high proportion of cases, specimens so obtained are unfit for microscopic study because of tissue distortion by the electric current. When the cutting current severs the pedicle of a bladder papilloma it is likely that it will also destroy evidence of infiltration into the underlying bladder tissue. Specimens obtained by cold resection are not subject to these disadvantages.

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NONOPERATIVE CURE OF VESICOVAGINAL FISTULA

FRANCIS A. BENEVENTI AND AARON J. GISSEN

The purpose of this paper is to report an instance in which a large vesicovaginal fistula was completely healed by simply placing the patient in a prone position with an indwelling catheter in position.

M. T., a forty-nine year old woman, was operated on at Roslyn Park Hospital for uterine fibroids, at which time a hysterectomy was performed. Five days later her bed was soaked with urine which was found to be escaping from the vagina. On cystoscopic examination a large opening was seen in the midportion of the floor of the bladder just proximal to the interureteric ridge. The fistulous opening was so large that the index finger of the right hand could be passed through the roof of the vagina into the bladder and be seen through the examining cystoscope. The wound edges were raw and weak, and these edges were made up of badly sloughing tissue which would require time for further sloughing before granulation tissue could be expected to grow. We felt that about three weeks should elapse before surgical closure of the fistula should be attempted. This would allow time for good strong tissue to grow. An indwelling catheter was then inserted into the bladder, and the patient was placed in a prone position in order to keep her as dry as possible.

Nineteen days later the patient and her bed were completely dry. She was now able to walk around (with an indwelling catheter) without spilling a drop of urine. She was then sent home with an indwelling catheter in place. After 28 days of catheter drainage, the catheter was removed. She was completely dry and continent, her only complaint being frequency of urination. On cystoscopic examination a week later the fistulous opening was found to be completely closed; however, the bladder capacity was small. A month later the bladder could hold 200 cc of water without pain; and now, seven months later, her bladder capacity is well over 300 cc. The bladder floor is sound.

On reviewing the literature, one is impressed by the fact that the highest rate of cure in vesicovaginal fistula is found in those patients who were operated on only once. Hence the first attempt is the best. There is no reported series of cases in which spontaneous healing occurred, although it is mentioned in the literature. Although we were very much surprised by the spontaneous healing of such a large opening which was so badly sloughed that it required time for good tissue to form, in going farther back in the literature we came upon A. J. Skene's book on *Diseases of the Bladder and Urethra in Women*, which was published in 1887. Here he states that the recommended treatment for intractable cystitis in the female is the construction of a vesicovaginal fistula in order to divert the urinary stream, "but the main difficulty," the book goes on to state, "has been to keep the incision open."

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VESICAL NECK OBSTRUCTION IN THE FEMALE: ETIOLOGY AND TREATMENT

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The development of the resectoscope has presented us with an instrument which has simplified the management of urinary retention in the female. The results of transurethral resection of the vesical neck in the female have been gratifying in general, but not all women so treated have been relieved. Emmett, Hutchins and McDonald[1] reported a series of 76 women with vesical neck obstruction treated by transurethral resection. Forty-six (60.6 per cent) were completely relieved; results were fair in sixteen (21.0 per cent) and poor in fourteen (18.4 per cent). Thirty-six women underwent transurethral resection for vesical neck obstruction at the Charles S. Wilson Memorial Hospital during an eight year period ending September 1953. Analysis of the results is as follows:

Amount of tissue resected:	*Number of cases*
0.5–1.5 gm.	30
2.0 gm.	5
5.0 gm.	1

Pathological findings in resected tissue:	*Number of cases*
Inflammation, fibrosis	31
Normal muscle and connective tissue	3
Glandular tissue and infection	2

Cystoscopic appearance of the vesical neck:	*Number of cases*
Pronounced bar or protruding tissue regarded as definitely obstructing	10
Moderate or questionable bar	14
No obstructing tissue at vesical neck noted	12

Number of resections per patient:	*Number of cases*
One resection	31
Two resections	5

Evaluation of the results of transurethral resection was sometimes difficult. Several women who had been relieved during the immediate, postoperative period had a recurrence weeks or months later. Other patients had no relief or aggravation of the urinary retention immediately after the operation, but gradually improved and had a satisfactory final result. Therefore, a distinction was made between early and late results. The condition during the first two months following the operation was taken as the basis for the immediate result; the condition more than two months after the operation was classified under late results. In some instances it was difficult to define what constituted a good result. If a patient continued to have subjective symptoms, but the residual urine had been

Accepted for publication January 27, 1954.

[1] Emmett, J. L., Hutchins, C. P. R. and McDonald, J. R.: The treatment of urinary retention in women by transurethral resection. J. Urol., 63: 1031, 1950.

substantially reduced, the result was classified as good, but in patients who had had only a small residual before the operation, persistence of symptoms was regarded as a poor result.

Result	*early (36 cases)*	*late (32 cases)*
good	25 (69.5%)	22 (70.0%)
fair	7 (19.4%)	5 (15.6%)
poor	4 (11.1%)	5 (15.6%)

Of the 32 patients followed for more than 2 months, the results changed as follows: From poor to good, 2; from fair to good, 2; from good to fair, 1; from fair to poor, 1; from good to poor, 2.

These findings bring up the following questions: 1) What is the etiology of vesical neck obstruction in women? 2) What treatment, if any, should be adopted for patients unrelieved by transurethral resection?

ETIOLOGY

Because transurethral resection relieves the vesical neck obstruction in most cases, the general trend has been to explain the obstruction by tissue of some sort protruding into the urethral lumen. The frequent cystoscopic findings of a bar or fold at the vesical neck seem to support this view, but similar changes are often seen in women with normal bladder function. Moreover, in many women with definite vesical neck obstruction cystoscopy shows an entirely normal bladder and there is nothing to suggest the nature of the obstruction. Histopathologic study of the vesical neck tissues has been of little help in clarifying the cause of the obstruction. The usual findings are varying degrees of inflammation, fibrosis, epithelial hyperplasia or hyperplasia of urethral glands. At times the specimen consists of normal muscle and connective tissue. Emmett, Hutchins and McDonald have come to the conclusion that the etiology of vesical neck obstruction and urinary retention in the female is not clear. They believe that numerous factors may be involved, none of which need to be of marked degree to tip the balance of power between the detrusor muscle and the vesical neck. Hutchins[2] has suggested that vesical neck obstruction may be caused by loss of normal relationship of bladder base to urethra. He has pointed out that descent of the bladder base and proximal urethra, with the distal urethra remaining in its normal position, may produce an angulation halfway down the urethra. To support his view he reports one case unrelieved following two transurethral resections and one case unimproved following a series of urethral dilatations. Both were relieved by repair of a moderate cysto-urethrocele.

Consideration of the urethral closure mechanism permits some conclusions with regard to the probable obstructive factors. Muellner and Fleischner[3] have shown that the chief factor in the normal closure mechanism of the female urethra is a high position of the posterior urethra and vesical neck. This results in a slight angulation at the urethrovesical junction which produces a valve effect at the vesical neck. Elimination of this valve effect by lowering of the bladder base and posterior urethra is necessary before the bladder can empty. Therefore, any process which interferes with the elimination of this valve effect will tend to produce urinary retention. Consequently, the following obstructive mechanisms should be considered:

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[2] Hutchins, C. P. R.: Vesical neck obstruction in women. J. Urol., 69: 102, 1953.

[3] Muellner, S. R. and Fleischner, F. G.: Normal and abnormal micturition. J. Urol., 61: 233, 1949.

1) Tissue protruding into the urethral lumen and causing an additional valve effect which persists in spite of adequate descent of the bladder base and posterior urethra. The treatment of choice would be transurethral resection.

2) Rigidity of the vesical neck or of its supportive structures may prevent adequate descent of the vesical neck which is essential to straighten the urethrovesical angulation. The probable cause of vesical neck rigidity is inflammation and fibrosis. Transurethral resection can be expected to be successful only if it can eliminate a co-existing, purely obstructive factor.

3) Excessive angulation at the urethrovesical junction or in the midurethra. As Hutchins has pointed out, even a minor relaxation of the supports of the bladder base can cause urinary retention if the urethra remains fixed in high position. On straining, the bladder base descends adequately, but the urethrovesical angulation does not straighten. A logical treatment would consist in repair of a cystocele if present. If no cystocele is demonstrable, a procedure should be used which would depress the vesical neck and posterior urethra. Little benefit can be expected from a transurethral resection.

4) Functional imbalance between the forces of expulsion (detrusor and abdominal muscles) and the forces of retention (pelvic floor muscles).

a) Weakness of the forces of expulsion: It is questionable whether weakness of the detrusor alone could be responsible for urinary retention because the expulsive force of intact abdominal muscles would be sufficient to overcome a normal urethral resistance. Therefore, in urinary retention associated with a hypotonic bladder, additional obstructive factors must be assumed. Such factors may be any of those mentioned above. A factor that should be considered in hypotonic bladders of neurogenic origin would be a disturbance of the reflex mechanism which causes the pelvic floor muscles to relax during micturition. Urinary retention observed in some debilitated and bedridden patients is probably caused by weakness of the abdominal muscles. These patients seem to be too weak to strain. As they regain their strength, they again use their abdominal muscles and the urinary retention disappears spontaneously.

b) Spasm of the pelvic floor muscles. Some neurogenic bladders belong in this category. In other cases the spasm is of a reflex nature, usually originating from a focus within the pelvis or lower abdomen. In still others, the spasm is produced by a psychosomatic mechanism. That pelvic floor spasm may be an obstructive factor is demonstrated by the observation that some patients are relieved, at least temporarily, by a pudic nerve block or by spinal anesthesia.

The logical treatment of urinary retention due to an imbalance between the forces of explulsion and those of retention would consist in the elimination of the cause for the imbalance. This, however, is not always possible nor practicable. Transurethral resection has been found reasonably effective where weakness of the detrusor was the main factor. Results have been poor where pelvic floor spasm was the chief cause of the urinary retention. A possible approach to the problem would be a procedure which would relax the pubovesical fascia which transmits the elevating effect of the pelvic floor muscles to the urethra and bladder base.

TREATMENT

Transurethral resection is the accepted treatment of vesical neck obstruction of uncertain etiology. However, a successful transurethral resection does not prove that obstructing tissue was actually present at the vesical neck; it only indicates that, irrespective of the obstructive mechanism involved, removal of tissue from the vesical neck reduced the urethral resistance to a degree sufficient for the relief of the obstructive symptoms. In the preceding chapter it has been shown that transurethral resection cannot be expected to produce a good result if vesical neck rigidity, urethrovesical angulation or pelvic floor spasm of a marked degree is responsible for the obstruction. Then relaxation of the structures supporting the vesical neck and posterior urethra may reduce the urethral resistance sufficiently for a satisfactory functional result. Based on these considerations, the following operation was devised:

The patient is placed in lithotomy position and prepared in the usual manner for vaginal procedures. The bladder is filled with 300 to 500 cc of sterile water. The amount of urethral resistance can then be roughly judged by manual compression of the bladder in an attempt to force the water through the urethra. A Young's prostatic tractor is passed into the bladder, the blades spread and gentle traction applied. The exact location of the vesical neck can be palpated at the angle between the shaft and the posterior blade of the tractor. A midline vertical incision is made in the mucosa of the anterior vaginal wall from a point about 1½ cm. below the external urethral meatus to a point about 1 cm. below the vesical neck. The incision is then carried through the pubovesical fascia in the same line. By combined blunt and sharp dissection the posterior and lateral walls of the posterior urethra and vesical neck are freed from the supporting fascia. Young's tractor is removed and manual expression of the bladder repeated noting the amount of infravesical resistance. Should the resistance still be marked, further liberation of the urethra and vesical neck is indicated. The pubovesical fascia can either be excised, left retracted or closed transversely. The vaginal mucosa is then closed using interrupted No. 000 chromic catgut sutures. A Foley catheter is anchored and the vagina packed. The pack is removed on the first postoperative day, the catheter on the third to fifth postoperative day. See figure 1.

CASE REPORTS

Case 1. A. L., female, white, single, aged 30, had been followed since childhood by the neurological service because of congenital, spastic diplegia involving both lower extremities. She had had multiple, corrective operations on both lower extremities. A neurinoma of the left posterior tibial nerve was removed on March 4, 1953. Following surgery it was noted that patient voided frequently and in small amounts. Residual urine varied between 400 and 900 cc. Urinalysis revealed mild pyuria; Staphylococcus aureus was cultured. Blood count was

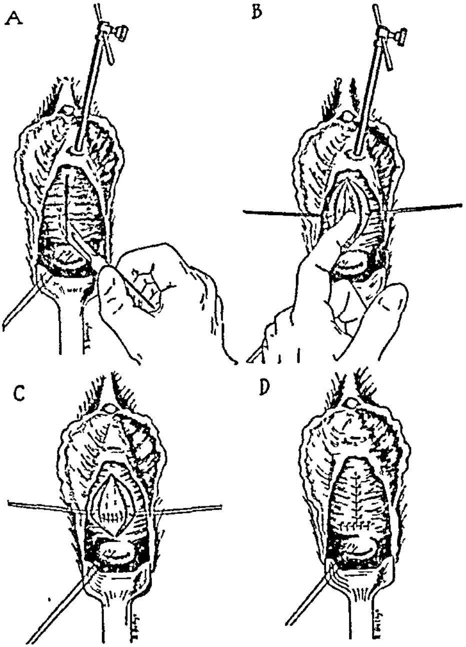

FIG. 1. *A*, line of incision *B*, vesical neck and posterior urethra freed from pubovesical fascia. *C*, transverse suture of pubovesical fascia (may be omitted). *D*, closure of vaginal mucosa.

within normal limits, nonprotein nitrogen was 34 mg per cent. An excretory urogram was negative. Pelvic examination revealed a markedly spastic pelvic floor, but was otherwise essentially normal. Cystoscopy showed trabeculation of the bladder with a few shallow diverticula. There was no evidence of organic obstruction at the vesical neck nor in the urethra. Cystometry revealed a hypotonic bladder with first desire to void at 600 cc, bladder capacity 900 cc and a maximum voluntary pressure of 44 cm. of water. Bladder sensibility to hot and cold was normal and the anal reflex was present. Following bilateral pudendal nerve block the residual varied between 125 and 300 cc and patient voided in amounts of about 350 cc. Three days after the pudic block, overflow incontinence developed and residual urine of 750 cc was recovered. On April 8, 1953 the afore-described operation was performed. A strip, about 3 cm. long and ¾ cm. wide, was excised from the pubovesical fascia. The catheter was removed on the fifth postoperative day. Immediately the patient voided spontaneously in amounts averaging 400 cc. Residual urine, determined daily for 10 days, varied between 70 and 280 cc. When last seen, on August 24, 1953, the patient had no special difficulty voiding and the residual urine was 180 cc. She is still under observation.

Case 2. J. P., female, white, para 2, aged 32, was first seen on April 14, 1953 complaining of marked difficulty in voiding, bloating of abdomen and occasional dysuria. These symptoms had developed immediately following a panhysterectomy and bilateral salpingo-oophorectomy in August 1952. Physical examination revealed a distended bladder 5 cm. above the symphysis. Pelvic examination revealed absence of uterus and cervix, a moderately tender vesical neck and slight bulging of the anterior vaginal wall, but no definite cystocele. Following catheterization the bulge in the anterior vaginal wall disappeared. Residual urine was 340 cc. The urine contained 4–6 pus cells per high power field; urine culture grew Escherichia coli. Cystoscopy revealed a normal mucosa and two moderate sized diverticula. No bladder neck bar or other, infravesical, obstructing factor was noted. Retrograde pyelogram was essentially normal. On April 16, 1953 two grams of tissue were resected transurethrally from the entire circumference of the vesical neck. The pathological report was fibromuscular tissue showing chronic, active inflammation. The catheter was removed on the third postoperative day and patient discharged 2 days later voiding freely in large amounts. Residual urine was 20 cc. Three weeks following the operation the obstructive symptoms recurred and a residual of 200 cc was obtained. Prolonged indwelling catheter, urethral dilatations and cholinergic drugs were ineffective. She was re-admitted on May 30, 1953. Urine contained 30–40 pus cells per high power field and B. proteus was cultured. A cystometrogram showed a normal curve with first desire to void at 400 cc and a maximum voluntary pressure of 62 cm. of water. Bladder sensibility to hot and cold was normal and the anal reflex was present. Residual was 750 cc. A bead chain cystogram, taken according to the technique described by Hodgkinson,[4] showed looping of the chain at the urethrovesical junction (fig. 2). This was interpreted as suggesting a valve-like, acute angulation between vesical neck and urethra. Operation, as described, was performed on June 5, 1953. In this case the pubovesical fascia was split longitudinally and then sutured transversely. The bladder catheter was removed on the fifth postoperative day. Subsequent studies failed to reveal any residual urine. A postoperative chain cystogram showed absence of the looping of the chain at the vesical neck. The patient was discharged 2 days later voiding with ease and perfect control. She has had no further difficulties during a follow up period of five months.

Case 3. M. Y., a white woman aged 25, was first seen in May 1950 complaining of frequency, dysuria and difficulty in voiding. She was a para 1, had had a Webster-Baldy type uterine suspension and appendectomy performed in 1939. Otherwise she had never been seriously ill. Pelvic examination revealed a tender vesical neck, endocervicitis and a tender, but othersise normal uterus and normal adnexa. All other findings were noncontributory. Urinalysis was negative. Cystoscopy showed mild urethrotrigonitis; retrograde pyelogram was essentially normal. Residuals were 45 and 60 cc. The patient then became pregnant for the second time and was delivered of a healthy child in February 1951. She was

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[4] Hodgkinson, C. P.: Relationship of the female urethra and bladder in urinary stress incontinence. Am. J. Obst. & Gynec., 65: 560, 1953.

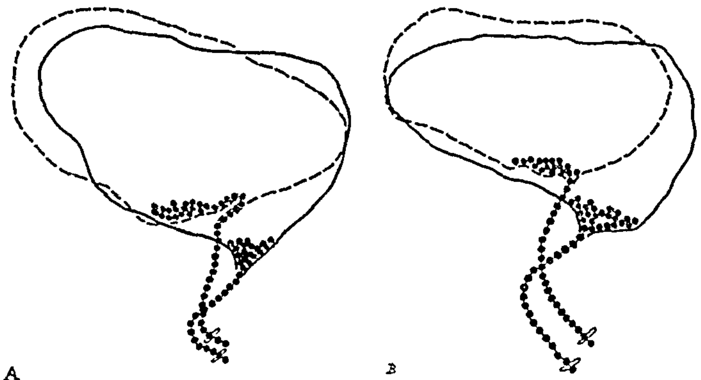

FIG. 2. Case 2. Tracing of bead chain cystogram. *A*, before operation. *B*, After operation. Interrupted line: Outline of bladder at rest. Solid line: Outline of bladder while straining to void.

seen again in March 1952 with essentially the same complaints as before. Pelvic examination revealed a cervical laceration and cervicitis, but was otherwise negative. Urinalysis was negative; residual urine was 50 cc. The cervicitis responded to routine treatment, but the obstructive symptoms persisted. Residual urine on successive visits was 70, 250 and 300 cc. Cystoscopy showed a slight, bar-like projection at the vesical neck which was regarded as a possible cause of the obstruction. On July 1, 1952 one gram of tissue was resected transurethrally from the vesical neck. Pathological report was chronically inflamed, sclerosed connective tissue. After the operation the patient did not feel relieved, but the residual urine was only 60 cc. Cystoscopy in October 1952 revealed a normal bladder and no apparent obstruction was noted at the vesical neck. A second transurethral resection was performed on October 16, 1952; one half gram of tissue was removed. Postoperatively, the residual urine was 60 cc, but the patient felt relieved. Obstructive symptoms recurred in February 1953. Urethral dilatations seemed to relieve the patient temporarily. Successive residuals were: 160, 0, 30, 40, 100, 130 and 150 cc. A bead chain cystogram taken while the patient was relaxed showed nothing that could explain the obstruction. However, a cystogram obtained while the patient was straining to void showed that the bladder base and posterior urethra did not descend adequately (fig. 3). This was interpreted as suggesting either pelvic floor spasm or fibrosis of the vesical neck and/or of the supportive structures. Operation for relief of urinary retention, as described, was performed on June 18, 1953. Under spinal anesthesia the bladder was filled with 400 cc of water. An attempted manual expression of the bladder was unsuccessful. After incision of the pubovesical fascia and liberation of the vesical neck and urethra the bladder could easily be emptied by manual compression. The pubovesical fascia was closed transversely and compression of the bladder was repeated. This time no water could be forced through the urethra. Therefore, the sutures were removed from

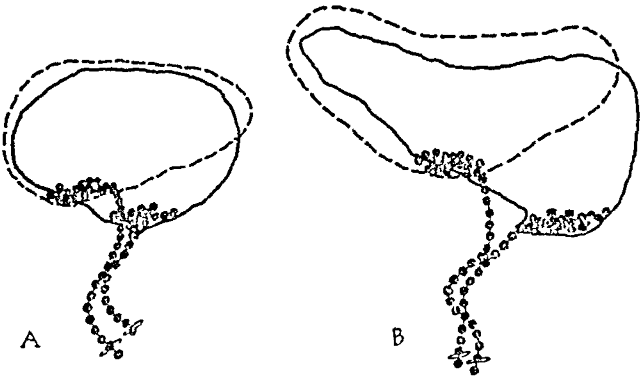

FIG. 3. Case 3. Tracing of bead chain cystogram. *A*, before operation. *B*, after operation. Interrupted line: Outline of bladder at rest. Solid line: Outline of bladder while straining to void.

the fascia and only the vaginal mucosa approximated. Immediately after catheter removal, on the fifth postoperative day, patient could void with ease and perfect control. There was no residual urine. Bead chain cystogram was repeated and this time the bladder base seemed to descend adequately during straining.

The patient was completely relieved for 18 days. Then she began to have low back pain, frequency and discomfort in the lower abdomen. She stated that she had no difficulty in voiding, but that the stream would suddenly shut off before she could completely empty her bladder. Residuals were 150 and 300 cc. Cystoscopy, performed 4 weeks after the last operation, showed a normal bladder mucosa. The inferior half of the vesical neck was occupied by a valve-like bar which had not been present prior to the last operation. Anterior to the bar the urethra appeared normal. Palpation of the urethra against the inlying panendoscope showed that the urethrovaginal septum was quite thin. The bar itself could be felt as a ring of considerable thickness. The bar was resected transurethrally on July 21, 1953. Two grams of tissue was removed. Pathological report was chronically inflamed, sclerosed connective tissue covered by stratified epithelium. Postoperatively the patient had difficulty voiding. Residuals were 200, 130, 0, 30 and 240 cc. Following the patient's discharge from the hospital the obstructive symptoms gradually diminished. On August 14, 1953 she still had some hesitancy while voiding, but the residual was 20 cc. On November 2, 1953 she reported feeling well with a nocturia of 3 the only complaint. There was no residual urine. Patient stated she felt better than at any time in the past 5 years. She is still under observation.

COMMENT

The histories of the three reported cases illustrate three different obstructive mechanisms. Pelvic floor spasm was the chief factor in case 1. This is suggested by the nature of the underlying disease, by the findings of a spastic pelvic floor and by the absence of any other demonstrable, obstructive factor. Urethrovesical angulation was the chief factor in case 2, but an additional spastic factor was also present. This is indicated by the absence of obstructive symptoms during the three weeks following the transurethral resection and by the observation that, under spinal anesthesia, just before the vaginal operation was begun, the bladder could easily be expressed manually. Rigidity of the structures supporting the bladder and urethra was the most likely cause of the obstruction in case 3. This is suggested by the inadequate descent of the bladder base before the vaginal operation, by the fact that the bladder could not be expressed manually under spinal anesthesia and by the recurrence of the obstruction following suturing of the pubovesical fascia.

An unusual feature was the development of a vesical neck bar 18 days following the vaginal operation in case 3. The mechanism is obscure. It is possible that the bar was formed by the retraction of muscle fibers and connective tissue of the vesical neck area after their attachments with the pubovesical fascia had been severed by the operation. Whatever the mechanism may have been, this observation suggests that some vesical neck bars in women may be caused by injury to the pubovesical fascia, presumably from parturition or surgery.

SUMMARY AND CONCLUSIONS

The results of transurethral resection, performed for vesical neck obstruction on 36 women, have been analysed.

The etiology of vesical neck obstruction in women has been discussed. Mechanisms which can cause vesical neck obstruction are obstructing tissue at the vesical neck, rigidity of vesical neck tissues, excessive urethrovesical angulation and functional imbalance between the forces of expulsion and those of retention. Several obstructive factors may be present at the same time.

Transurethral resection of the vesical neck is the most effective, single procedure for the relief of urinary retention of obscure etiology in the female. About 18 per cent of the patients so treated are not relieved in spite of multiple resections.

A new operation for the relief of vesical neck obstruction in the female has been described. This operation is indicated in those patients who have no demonstrable cystocele and are not relieved by transurethral resections or in whom no relief can be expected from a transurethral resection.

Three cases in which this operation was employed have been reported.

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EFFECT OF PUDENDAL NERVE OPERATIONS ON THE NEUROGENIC BLADDER

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Previous publications dealt with the technique, indications and results which were obtained by treating cord bladder dysfunction with pudendal nerve anesthesia or pudendal neurotomy. In the following, the experience with pudendal nerve interventions is presented on 29 patients with cord bladders.

MATERIAL, PROCEDURES AND RESULTS

All patients had signs of upper motor neuron lesions which were caused in 25 cases by trauma, in 3 cases by arachnoiditis and in 1 case by partial aplasia of the sacrum. Five patients had cervical and the remaining 24 had thoracic lesions.

Fifty operations were performed, 23 of which were neurotripsies and 27 were neurotomies. Twenty-one patients underwent bilateral and 8 unilateral operations. The exposure of the pudendal nerve followed the approach as described elsewhere. The anatomical findings at the site of operation are presented in table 1. The pudendal nerve is, in the majority of cases, divided into two branches of which the medial is usually stronger than the lateral; then follows the incidence of one solid nerve trunk and least frequently can three branches be differentiated beneath the sacrotuberous ligament.

The overall results, including the relationship to the level of the lesion, are reflected in table 2. Twenty-two patients benefited from pudendal interventions, while 7 failed to do so. The majority of cervical lesions belonged to the group of failures, although all had bilateral procedures. Unilateral procedures were beneficial in 7 out of 8 cases.

Tables 3 and 4 reflect the number of cases which underwent neurosurgical interventions alone, as contrasted with the patients who had additional transurethral resections of the vesical neck. Out of a total of 11 patients, 8 (or ¾) benefited from the nerve operations alone. Among the 18 patients who underwent a combination of transurethral resection with nerve operations, 14 regained a balanced bladder function.

The effect of pudendal nerve intervention on the sexual function is illustrated in table 5. It can be seen that generally a change takes place in the majority of patients and that it is more pronounced with bilateral than with unilateral operations.

DISCUSSION

The rationale of all procedures directed at the pudendal nerve was discussed elsewhere, and is based upon the reciprocal innervation between the striated muscles of the pelvic floor and the detrusor of the bladder.

Of the 29 patients, 22 benefited from the operation. This compares favorably

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Read before Section of Urology at meeting of California Medical Association, Los Angeles, Calif. May 24 through 27, 1953.

TABLE 1 *Anatomical findings in 50 dissections*

Large Solitary Trunk	Medial and Lateral Branches	Medial Intermediate and Lateral Branches
16 Instances	23 Instances Small lateral 16 Equal size medial and lateral 4 Small medial 3	11 Instances

TABLE 2 *Results of all patients*

	No of Patients	No of Operations	Good	Poor
Cervical lesions				
bilateral	5	10	1	4
Thoracic lesions				
bilateral	16	32	14	2
unilateral	8	8	7	1
Total	29	50	22	7

TABLE 3 *Results of 11 patients without additional transurethral resections*

	Good	Poor	Total
Bilateral pudendal operations	6	2	8
Unilateral pudendal operations	2	1	3
Total	8	3	11

TABLE 4 *Results of 18 patients with additional transurethral resections*

	TUR preceding Nerve Operation		TUR following Nerve Operation		TUR preceding and following Nerve Operation		Total	
	Good	Poor	Good	Poor	Good	Poor	Good	Poor
Bilateral	6	4	2	—	1	—	9	4
Unilateral	5	—	—	—	—	—	5	—
Total	11	4	2	—	1	—	14	4

with the experience of Ross, who observed 8 good results out of a total of 11 cases The fact that transurethral resection preceded the destructive nerve operation in the majority of our combined procedures, illustrates the endeavor to choose nerve surgery as the last resort It should be stressed, however, that pudendal nerve anesthesia which has been applied in many hundreds of cases, is used freely in combination with transurethral resection with good results, either preceding or following this operation Especially a combination of nerve operations with tenotomy of the anterior lip seems promising, since striated fibers could be demonstrated in the resected tissue of that location

Where unilateral pudendal nerve interruption was carried out, the operation

TABLE 5. *Effect of pudendal nerve operations on sexual function (erection) of 29 patients*

Changed			Unchanged			Undetermined
From complete to absent	9		Complete	6	(4 unilateral)	1
From complete to partial	5	(2 unilateral)	Partial	2	(1 unilateral)	
From partial to absent	2		Absent	4		
Total	16			12		1

was performed on that side which was governed by the major cerebral hemisphere. An interesting fact is that among these cases there was that of a young boy of 7 years* with a partial aplasia of the sacrum, who showed upper motor neuron signs with hyperreflexia and pathological toe signs, a fact which has been repeatedly observed in children with this type of congenital anomaly, by one of us (E. B.).

The anatomical findings suggested Tavel's anomaly in three dissections in which a larger lateral branch (dorsalis penis nerve) than a medial branch (deep perineal nerve) was found. Presumably, based upon previous experience, this large lateral branch may have supplied the ischio- and bulbocavernosus muscles and the sphincter urethrae. In four additional dissections both branches were of equal size, and since no stimulation was performed it remains undetermined whether one dealt in these instances with Tavel's anomaly; it would seem advisable to stimulate the lateral branch only then when the medial branch has been severed, in order to identify whether or not efferent fibers are present in the lateral branch which cause a contraction of the ischio- and bulbocavernosus muscles on an electric stimulation. However, one must bear in mind that stimulation of afferent pathways in the intact lateral branch may precipitate, through synapses at the respective cord segment, a mass reflex of the pelvic floor which, in turn, may simulate a reaction closely resembling that obtained from stimulation of the efferent fibers of the lateral branch. For this reason, evidence of which has been previously presented, stimulation was not undertaken routinely.

While it is easily understandable that erection remains unchanged more often with unilateral nerve interruption than with bilateral, it remains unexplained why no change occurred in three cases with bilateral interruption. The earlier explanation—namely, that fibers may have been overlooked, appears no longer valid with the growing experience gained from an increasing number of dissections. Our conjecture would be that either peripheral ganglia, located in the penis, take over this function on direct stimulation, or that some regeneration of the severed nerves has occurred.

In analyzing the 7 failures, we must omit 1 patient with a thoracic lesion who succumbed suddenly and unexpectedly to his pulmonary tuberculosis after a unilateral pudendal neurotomy. This leaves 6 cases of which 2 patients had thoracic and 4 patients had cervical lesions. Both cases with thoracic transections had an equivocal result in that they were able to retrieve a balanced bladder function for some time on and off. The greatest handicap for one of the two patients was severe spasticity of his abdominal muscles which accompanied his T-2 lesions. He could not exert abdominal pressure because of his high lesion without an abdominal binder, but even then severe spasticity of the abdominals interfered with the application of Credé pressure. His detrusor had good tone, but lacked uninhibited contractions essential for reflex micturition. He had a good result for approximately 3 months. A recent checkup disclosed renewed activity of the bulbocavernosus reflex, suggestive of nerve regeneration. The other patient with a T-10 lesion had a well functioning reflex bladder for 5 years prior to any intervention, which became imbalanced following a urinary infection and right nephro-ureterolithiasis. Following removal of the stones and repeated transurethral resections which did not correct his bladder function, a bilateral pudendal neurotripsy restored the function for a period of three months. Thereafter, the bladder became imbalanced and the bulbocavernosus reflex returned, again suggestive of regeneration as in the preceding case. In addition, the patient admits that he has not adhered to a "bladder hygiene", i.e., regulating fluid intake and urination around the clock. Urinary infection and return of pudendal nerve function are probably responsible for this failure. Inasmuch as both these patients had neurotripsies it seems as if neurotomies would be a more reliable procedure to prevent recurrence.

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* We want to thank Doctor Tracy O. Powell for permission to incorporate this case in our report.

The remaining 4 patients had significantly cervical cord lesions. Although their bladder function returned to some degree after the operation, it remained poorly balanced, i.e., the residual exceeded 20 per cent of the bladder capacity. The causes for that were threefold: Lack of hand function sufficient to exert a Credé maneuver, lack of uninhibited waves strong enough to produce an emptying contraction despite the presence of a good detrusor tone, or severe spasticity of the abdominal muscles, interfering with the execution of extrinsic pressure or upsetting intrinsic diaphragmatic pressure. Any single one or a combination of these factors was responsible for the failures; however, it is felt that the most important is the condition of the detrusor because the one patient with the cervical injury, who benefited from bilateral pudendal neurotripsy, had at all times a well functioning bladder muscle with strong emptying contractions.

COMMENT ON INDICATIONS AND CONTRA-INDICATIONS

In view of this experience, the following requirements are necessary for operative indication: a) If the patient has command of his hands (including high thoracic lesions), no abdominal spasticity should be present strong enough to make Credé pressure impossible. b) If the patient is tetraplegic and, therefore, unable to perform the Credé maneuver, a well functioning detrusor muscle should be present with emptying uninhibited contractions. c) Severe urinary infection with or without calculosis must be absent. d) Structural contracture of the vesical neck or other obstructive uropathy must be absent. e) Each of a series of 6 pudendal anesthetic nerve blocks should produce a satisfactory result and at least one of them, preferably the last, should be combined with cystometric examinations which precede and follow the nerve anesthesia.

In addition to these requirements, there are yet other factors to be considered.

In the presence of sexual function, i.e., erection, preferably a unilateral procedure should be performed. Inactivity, of whatever cause, of the conus terminalis is an absolute contra-indication for any pudendal intervention. Bilateral operations should be performed in stages 2 to 3 weeks apart in order to evaluate the result of the first operation. In right-handed individuals, the right pudendal nerve should be first attacked. There is no clinical evidence that different results are obtained from neurotomies than from neurotripsies.

SUMMARY

Twenty-three pudendal neurotripsies and 27 pudendal neurotomies (a total of 50 interventions) were performed on 29 patients with upper motor neuron lesions of the spinal cord in order to correct bladder dysfunction. Five patients had cervical and 24 had thoracic lesions, 3 of which were due to arachnoiditis, 1 was associated with a partial aplasia of the sacrum and 25 were of traumatic origin. Eighteen patients were subjected to a combination of pudendal nerve intervention and transurethral resections, with 14 good and 4 poor results. Eleven patients without transurethral intervention had 8 good and 3 poor results from pudendal nerve operation alone. Twenty-one patients had bilateral pudendal operations with 15 good results and 6 failures. Eight patients had unilateral interventions with 7 good results and 1 failure. The anatomical findings at the site of exposure and the effect of the operation on erection are discussed. The rationale of the operation is mentioned and the causes of failure are analyzed. Indications and contra-indications are presented in detail.

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ABACTERIAL URETHRITIS: A REPORT OF EIGHT CASES WITH ISOLATION OF THE PLEUROPNEUMONIA-LIKE ORGANISM

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INTRODUCTION

Abacterial urethritis has often been a problem in the practice of military medicine. The reporting of urethritis due to venereal etiology (i.e., gonococcal) makes it more imperative to establish the cause of each case of urethritis. Williams[1] noted that nonspecific urethritis was responsible for the bulk of hospital admissions for common venereal diseases among Australian troops in Borneo. Others have estimated that among Australian troops 45 to 60 per cent of cases of urethral discharge were caused by some agent other than Neisseria gonorrhoeae.[1] Only following the comprehensive writing of Dienes et al.[2] has it been appreciated that there is a significant relation of the pleuropneumonia-like organisms to so-called abacterial urethritides.

These organisms have been incriminated as the cause of bovine pleuropneumonia, agalactia in goats and sheep, and arthritis in mice and rats. In human studies, Dienes et al.[2] were able to isolate the organism from cervical secretions of 26 per cent of 214 women. Of this group (26 per cent) only 8 were free of genito-urinary disease and the remainder were associated with such disturbances as leukorrhea, trichomonal infection and gonorrhea. In 11 cases associated with gonorrhea, these organisms persisted after the gonococci disappeared. This led to the assumption that these organisms are a part of the flora of the female genital tract with potentialities of pathogenicity under certain conditions. In male patients only an 8 per cent incidence was noted; but in 58 male patients in which the organism was found, all had evidence of prostatitis or other genito-urinary tract infection at the time of isolation of the organism. In this group of 58 male patients, 4 had hemorrhagic cystitis and 27 had arthritis of varying type and severity with 18 being an acute migratory type. Of these 18 cases of acute migratory arthritis, 9 presented the typical picture of Reiter's syndrome.

In 1943, Beveridge[3] reported the isolation of pleuropneumonia-like organisms from 4 of 24 cases of nongonoccal urethritis in men. In 1945, Johnston[4] reported the isolation of pleuropneumonia-like organisms, in both of which intra-epithelial inclusion bodies were found, from two cases of urethritis which could not be attributed to gonorrhea by bacteriological and serological studies.

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Reported with permission of Surgeon General, USAF. Views expressed are those of the
official opinions of the Surgeon General's Office.

Australia, 1: 693–695, 1946.

W., Smith, W. E., Madoff, S. and Bauer, W.: New Eng. J. Med.,
8.

[3] Beveridge, W. I. B.: Med. J. Australia, 2: 479–481, 1943.

[4] Johnston, G. A. W.: Med. J. Australia, 1: 368–371, 1945.

Harkness and Hendersonbegg[5] found 36 of 253 cases of nongonococcal urethritis (including cases associated with arthritis) to be positive for the pleuropneumonia-like or L organism in the male, by culture. They found seven out of 41 cases of polyarthritis associated with abacterial urethritis to be positive for the L organisms. In 46 females suffering from nongonococcal cervicitis or vaginitis, 12 were found to be positive for the L organisms. In 139 cases of acute gonorrhea in the male, 12 were found to be positive for the L organism. Three of 18 females with acute gonorrhea also were found to be positive. Fifty normal males gave negative results from urethral washings as did 15 normal females from cervical and vaginal swabs. Three of seven female contacts of men with the disease were found by cultures to be positive for the L organisms.

Recently, Slingerland and Morgan[6] have reported a case of sustained bacteremia postpartum in a 16-year-old Negress due to the pleuropneumonia organism which was also isolated from the cervical secretions during the first 24 hours of fever. Nine positive blood cultures were obtained over the first 24 hours of fever indicating a true sustained bacteremia. The patient recovered with penicillin and streptomycin therapy in spite of insensitivity to these drugs being indicated by *in vitro* studies and was asymptomatic with negative blood cultures on several follow-up examinations.

In a recent report of 23 cases of Reiter's syndrome, Hall and Finegold[7] isolated the pleuropneumonia-like organism from only one of eight patients examined. However, their culture medium was veal infusion agar plus 50 per cent horse serum and the positive results might have been increased if the culture medium had been enriched with 20–40 per cent human sera or human ascitic fluid since these materials are supposedly more favorable for growth of the organism.

BACTERIOLOGY[2, 3, 8]

The exact place of these organisms in the bacteriological classification has not been established. They have some characteristics of viruses. The distinguishing characteristics of this group are 1) inability to stain with ordinary bacterial stains but demonstrable with prolonged staining by Giemsa's stain, 2) inability to grow on ordinary media but producing a characteristic colony on media enriched with 10 to 40 per cent human serum or human ascitic fluid, 3) great pleomorphism with ring forms, elementary bodies, spherules, branching filaments and polar-staining bacillary forms, and 4) filtrability through gradacol membranes down to about 0.4 μ pore diameter.

Reproduction has been observed by spherule, granule and filament formation with surface and subsurface colony growth. Because of the filament formation and branching, the generic name of Asterococcus has been proposed for the pleuropneumonia group.

The individual colonies may vary from 10 to 600 μ in size but often attain the average size of 20–60 μ. Animal strains of the organism must be incubated at 37° for 3 to 5 days for typical colony growth. A small agar square is removed for examination and placed on a cover glass to which has been applied Diene's methylene blue-azur stain (dried or wet). This is placed on a slide and examined microscopically. The colonies may be surface or subsurface in location and typically show a dark staining center with a clear membrane-like periphery in which may be seen bacillary forms, globoid bodies and clear vacuoles.

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[5] Harkness, A. H. and Hendersonbegg, A.: Brit. J. Vener. Dis., 24: 50–58, 1948.

[6] Slingerland, D. W. and Morgan, H. R.: J.A.M.A., 150: 1309–1310, 1952.

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[8] Zinsser's Textbook of Bacteriology. New York: Appleton-Century-Crofts, Inc., 1948, 9th ed., pp. 640–649.

THERAPY

Initial investigations had noted insensitivity of these organisms to sulfonamides and penicillin. Leberman et al.[9] investigated the sensitivity of these organisms to aureomycin, chloramphenicol, dihydrostreptomycin, streptomycin and sodium penicillin G. Streptomycin was the only antibiotic effectively inhibiting all of the strains tested. Only two strains showed resistance at a concentration of 5 mg. per ml. of medium. Dihydrostreptomycin did not exhibit such inhibitory action. High concentrations of aureomycin and chloramphenicol were necessary to inhibit most strains. Penicillin was found to be ineffective for any of the strains at concentrations such as 1000 units per ml.

METHODS AND MATERIAL

Normal males on active military duty were the subject material. All cases were originally seen in the out-patient venereal disease clinic where means were taken to exclude gonorrhea and other causes of a urethritis by appropriate methods of examination. Those cases with positive urethral exudate cultures on tryptose blood agar base* (enriched with 20 per cent sterile normal human serum), stained by Diene's methylene-azur stain,† were admitted to the medical ward. In addition those cases of abacterial urethritis of unknown cause, who were therapeutic problems, were also admitted to the ward. Over a period of 27 months 179 cases of gonococcal urethritis were encountered. During this period 17 cases of urethritis due to the pleuropneumonia-like organism were encountered. The original records of only 8 patients were available for review: therefore only these 8 cases are reported. During this same interval 6 cases of urethritis were encountered, nonvenereal, cause undetermined and one case of urethritis, bacterial, due to Diplococcus paleopneumoniae and Micrococcus pyogenes.

No explanation is readily available for the relatively low incidence of abac-

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[9] Leberman, P. R., Smith, P. F. and Morton, H. E.: J. Urol., 64: 167–173, 1950.

* *Enriched culture* agar base; concentration percentage:

Bacto-tryptose	1.0
Bacto-beef extract	.3
NaCl	.5
Agar	1.7
	20.0
	100.00 ml.

† Diene's stain:

Methylene blue	2.5 gm.
Azur II	1.25 gm.
Maltose	10.0 gm.
Na_2CO_3	0.25 gm.
Distilled water	100.0 ml.

terial urethritis with reference to proven cases of gonococcal urethritis as contrasted to the previous incidence as given by Australian writers. All eight of these patients were free of arthritis and were in relatively good physical condition excepting the urethral discharge. None presented any semblance of Reiter's syndrome. Four were of an acute variety and four were of a chronic variety. One was treated for latent syphilis, because of a history of 130 injections for a positive serology in 1945, and the presence of an elevated serology titer on admission of 1:32. The urethral discharge varied from a whitish milky type to a profuse greenish-yellow type, being more profuse in the acute cases. All responded to treatment and were discharged from the hospital. Unfortunately due to loss of contact with the patients relative to peculiarities of transfer and duty assignments in the military service, follow-up studies to determine the incidence of recurrence are not available.

ABBREVIATED CASE REPORTS

Except as indicated in the preceding section, all eight of these patients were relatively free of any other organic disease. Routine laboratory examinations were normal and routine physical findings were noncontributory. Therefore, the cases will be reported in brevity:

Case 1. D. A. P., W.M., aged 29, was admitted with a history of a urethral discharge for 12 days. Serology and gonococcal studies were negative. He was treated with 5.0 gm. of streptomycin over a 5 day period and the urethral discharge subsided. On the fourth day of hospitalization acute bronchitis developed. A total of 3,600,000 units of penicillin was given. The patient was discharged asymptomatic after 10 days' hospitalization. He gave a history of having gonorrhea in November 1949, approximately five months before this acute attack of nongonococcal urethritis due to the pleuropneumonia-like organism.

Case 2. E. D. B., W.M., aged 21, gave a history of having gonorrhea in November 1949 and receiving two injections of 300,000 units of penicillin. The smears became negative for gonococci but the discharge persisted. Due to this he was treated with sulfadiazine without avail. Symptoms persisted for approximately six months at which time a culture for the pleuropneumonia-like organism was positive and he was admitted for treatment. Over a six day period he received 8.0 grams of streptomycin and was discharged asymptomatic.

Case 3. M. K. W., W.M., aged 26, gave a history of originally having gonorrhea in 1949 at which time he was treated with 300,000 units of penicillin. The discharge completely subsided but recurred in 4 days and at that time the gonococci could not be found in the urethral exudate. He was treated with sulfadiazine and local irrigations without improvement. Later he was given prostatic massages without avail. Because of the persistence of a discharge over a 5½ to 6 months period he was studied for pleuropneumonia-like organisms and the culture was positive. His serology and smears for gonococci were negative at that time. He was admitted to the hospital and treated over a 6 day period with 8.0 gm. of streptomycin. He was discharged asymptomatic.

Case 4. C. E. M., W.M., aged 29, gave a history of a recurring urethritis since

1946. He denied venereal diseases and his serology was negative. The pleuropneumonia-like organism was cultured and examination for gonococci was negative. He was admitted to the hospital and treated over a 5 day period with 5.0 gm. streptomycin and 30.0 gm. sulfadiazine. He was discharged asymptomatic.

Case 5. H. A. R., C.M., aged 26, gave a history of a chronic discharge since 1945 (5 years). In February 1950, approximately 5 months prior to admission, he had a gonococcal urethritis that was treated with penicillin. Because of the persistent discharge he was studied for pleuropneumonia-like organisms and the culture was positive. Serology and smears for gonococci were negative. He was treated over a 9 day period with 9.0 gm. of streptomycin and discharged asymptomatic.

Case 6. W. S. McK., W.M., aged 23, presented as a case of acute urethritis with no significant venereal history and negative studies for the usual venereal diseases. He was found to have positive cultures for the pleuropneumonia-like organism and was admitted and treated over a 3 day period with 2.5 gm. streptomycin and 12.0 gm. sulfadiazine. He was discharged asymptomatic.

Case 7. J. W. P., C.M., aged 23, was seen with a history of a discharge of 1 week's duration. He denied venereal diseases but had a sex contact 2 months prior to onset of the discharge. His serology was negative and smears were negative for gonococci. His cultures were positive for the pleuropneumonia-like organism. He was admitted and treated over a 7 day period with 9.0 gm. streptomycin and 40.0 gm. of sulfadiazine. His discharge cleared and he was dismissed from the hospital asymptomatic.

Case 8. C. T., C.M., aged 21, was seen with the complaint of a recent onset of a whitish mucoid discharge. There was no recent history of an exposure contact. He had been treated with 130 injections in 1945 for a positive serology. His studies for gonococci were negative but his serology titer was 1:32. His cultures were positive for the pleuropneumonia-like organism. Over a 10 day period he was treated with 10.5 gm. streptomycin and 46.0 gm. sulfadiazine. His discharge abated and then he was given 6,000,000 units of penicillin based on a diagnosis of syphilis, latent, seropositive only. He was discharged from the hospital asymptomatic.

DISCUSSION

Three cases (Nos. 2, 3, and 5) revealed a direct onset following acute gonococcal urethritis with subsidence of the gonococcal infection as revealed by negative smears but with immediate recurrence or persistence of the discharge. Two of these cases (Nos. 2 and 3) did not respond to sulfadiazine after the smears became negative for gonococci following penicillin treatment of the gonococcal urethritis. One case (No. 1) had a 5 months lapse between the recurrence of a discharge and treatment for an acute gonococcal urethritis. One case (No. 7) had a sex contact 2 months prior to onset of the discharge. Three cases (Nos. 4, 6, and 8) gave no history of recent sex contact or recent gonococcal urethritis preceding the onset of the discharge. These observations are in accord with previous investigations and suggest a venereal transmission of this disorder.

Two patients (Nos. 2 and 3) treated with sulfadiazine prior to isolation of the organism showed no response to this drug. Four patients treated with streptomycin alone (Nos. 1, 2, 3, and 5) showed a good response to treatment. This is in accord with prior observations and suggests that the good response in four patients (Nos. 4, 6, 7, and 8) treated with streptomycin-sulfadiazine therapy was due to streptomycin and not to sulfadiazine.

SUMMARY

Eight cases of nongonococcal or abacterial urethritis, with isolation of the organism referred to as the pleuropneumonia-like or L organism, have been presented.

Evidence suggests that this is a venereal transmitted disorder.

Streptomycin appears to be effective in this condition.

Reference has been made to significant medical literature on this subject.

It is recommended that cases of urethritis of a nongonococcal or abacterial nature be investigated with reference to isolation of the pleuropneumonia-like or L organism.

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TREATMENT OF HYPOSPADIAS: TEN YEARS' EXPERIENCE WITH TUNNEL-GRAFT URETHROPLASTY

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In 1948 the senior author (Havens) with A. S. Black outlined his program for the management of hypospadias, described in detail the technique of tunnel-graft urethroplasty, and reported results for a five-year period.* Now, after another 5 years of experience with the same methods, we present a report covering the entire ten-year period. We shall not omit a single case that came under our care and we hope that by giving such a detailed report, others will be able properly to assess the value of the methods employed.

We have continued to employ the two-stage Edmunds' procedure for the correction of chordee and have been pleased with the results achieved by its use. We have accepted for correction of the chordee any patient 4 years of age or older. Tunnel-graft urethroplasty has not been undertaken for any patient younger than the age of 15.

There have been only minor changes in the technique of tunnel-graft urethroplasty as described in the earlier paper and as illustrated here. In the original article it was stated that the graft was put in on a size 22F catheter. We now prefer to use a size 24F catheter. It was also stated that the catheter bearing the graft was anchored by a suture near the posterior lip of the channel. Recently, we have anchored this catheter by transfixing it with two stainless steel wires. Each transfixes the catheter from side to side and one is made to pass through the glans while the other is placed near the posterior lip of the channel.

In the previous paper it was stated that stilbestrol was used for the purpose of controlling erections. In the last 5 years we have discontinued entirely the use of this drug. Our present plan for sedation is not different from that which might be used after appendectomy or herniotomy.

In the 1948 report it was stated that the requirements for a "good result" were, first, that the patient be able to have satisfactory sexual intercourse; second, that he have a urethra of adequate caliber without hairs or sacculation; and third, that the urethral opening be at or very near the tip of the glans penis. We have continued to adhere strictly to these requirements and all patients that have been listed as having a good result have met these requirements.

RESULTS AND COMMENT

December 31, 1952 was the last day of our ten-year period, and the status of our series of cases as of that date is shown in the table. It should be noted that 10 patients remain under our supervision awaiting the proper time for completion

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Read at the meeting of the American Medical Association, New York, N. Y., June 1 to 5, 1953.

* The technique is illustrated in the *Journal of Urology*, 1949, vol. 61, p. 1053.

TABLE 1. *Report on all patients who have come, during a ten-year period, to the surgical service of one of us (Havens) for treatment of hypospadias*

	CASES		
Patients still under age of puberty			55
Minor problems corrected		4	
Minor problems, further treatment planned		2	
Major hypospadias,* correction to be completed at puberty			
First stage only for correction of chordee		7	
Correction of chordee completed		42	
Adults treated for major hypospadias			77
Correction of chordee only		5	
Minor probems corrected (after repair by others)		3	
Completion (by other methods) of repair begun by others		4	
Tunnel-graft urethroplasty		65	
Left our care	8		
Still under treatment†	10		
Good result	46		
Fair result	1		
Total			132

* We use the term "major hypospadias" to include all cases of hypospadias in which chordee is present.

† Seven of the 10 patients who were still under treatment at the time this paper was written have since completed treatment with good results.

of their treatment. In each of these 10 cases there remains only one further stage to be done and we have good reason to believe that each patient in this group will have a good result. When sufficient time has elapsed so that final reports of these cases can be given, the tabulation should show 56 good results or 86 per cent of the 65 cases under consideration.

Of the 8 patients who left our care we are confident that at least 5 of them could have been completed with good results. These 5 cases must be listed as failures, not because of any fault in the method of treatment but perhaps because of our own shortcomings in the art of the practice of surgery—we failed to hold the confidence of these patients. If these could have been added, the percentage of good results would have risen above 90 per cent. Our considered opinion of the tunnel-graft method is that by using it, we can offer the boy who has hypospadias a 90 per cent chance for a good result.

For the treatment of hypospadias by the method we have employed, a minimum of 4 operations is necessary (2 for the correction of the chordee and 2 for the urethroplasty). Not more than 4 operations were required for most of those patients who had penoscrotal hypospadias, who came to us at or beyond the age of puberty, and who had undergone no previous surgical treatment. Those patients who had had previous treatment usually needed one or more additional operations as did also those who had midscrotal or perineoscrotal hypospadias. For all patients whose treatment has been completed, the average number of operations was 5.5.

From articles written about the treatment of hypospadias and from comments heard during informal discussions of the subject, the senior author (Havens) has gained the impression that the occurrence of fistulas in the course of repair of hypospadias is feared more than it need be and is given undue consideration as a criterion of the advantage or disadvantage of any given method. We have had fistulas in 18 of our 46 completed cases (usually only 1) and we have been unhappy when they appeared. We have had no difficulty in repairing them, however; they have been an annoyance, of course, because they delayed the completion of the repair, but nothing more.

We retain the opinion expressed in the previous report that it is not necessary to complete the repair of hypospadias before school age in order to avoid psychopathic problems. Approximately half of our patients who had reached or passed the age of puberty had had unsuccessful (1 to 20) operations in childhood and the remainder had had no treatment prior to the age of puberty. We observed no psychic problems of importance in any of them. All these patients have fitted normally into society and not one, to the best of our knowledge, has failed to become a self-respecting, self-supporting citizen. Several of these patients are making better than average progress in their careers. For example, among our former patients we have a doctor, a dentist, an architect, a research chemist, a medical technician preparing for medical school, a college student who excels in extemporaneous public speaking and debate, and several who hold responsible positions in business. Many have married, and we know of 4 who have from one to four children.*

We are not disturbed about the alleged problem of readjustment in those cases in which the patient has been raised as a girl. We have had 8 such patients, all of whom lived as girls until or beyond the age of 14 years. Four returned to their home communities after treatment and later told us that they found the readjustment to be no particular problem. Two others are happily married, and only 2 made it a special point to avoid returning to their original homes.

Of the 8 patients who were raised as girls, 3 were true hermaphrodites, and 2 were pseudohermaphrodites (1 male, 1 female). The remaining 3 were males who had perineoscrotal hypospadias and simply had been mistaken for females.

CONCLUSION

We repeat the statement made in an earlier paper that we do not agree that correction of hypospadias need be urged at an early age in order that the patient may not become a psychopath. Our observation of numerous patients who did not receive proper or any treatment at an early age does not substantiate any such opinion.

We repeat also our statement previously made that restoration of normal

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* The second-born of 1 of our patients was a boy who also had hypospadias. We have heard of no other instance in which a hypospadiac father begot a hypospadiac son.

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Z-PLASTY FOR CORRECTION OF MEATAL URETHRAL STRICTURE FOLLOWING HYPOSPADIAS REPAIR

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The complications associated with the plastic repair of hypospadias are well known Recently we have encountered two patients who presented the complication of meatal urethral stricture

It was mandatory that the stricture be corrected before further surgical repair. In both cases a wide meatotomy with careful suture of the mucosal margins to the surrounding skin was carried out only to be met with complete failure due to circular scar contracture

In any case where this complication occurs diversion of the urinary stream by the perineal or suprapubic route is necessary We prefer the former, because it is simpler to perform, and the incidence of bladder spasm with resultant complication is much less than with the suprapubic method

To solve these problems a Z-plastic procedure was employed interdigitating small flaps of adjacent skin into longitudinal incisions made about the circumference of the urethra at the site of stricture In both cases the final results were excellent

TECHNIQUE OF OPERATION

For the correction of this complication the principle of the multiple Z plastic procedure was applied The central member of each Z is on the circumference of the circular scar and the arms of the Z are cut at 60° angles and are equal in length to the central member In this instance instead of having a straight line contracture as in most cases where the Z plastic is applicable we have a circular contracture The central member of each Z is a portion of the circumference of a circle After the flaps are transposed a significant increase, approximately ⅓, in the circumference of the circle is immediately appreciated In addition an offset scar is created which minimizes subsequent contracture and eliminates the purse string contracture which was the cause of the original failure See figure 1

The external genitalia are thoroughly cleansed with phisoderm both the night before and immediately preceeding the operation A circular incision is then made through the skin and subcutaneous tissues about the strictured urethral meatus The distal end of the urethra is mobilized by blunt dissection of the peri-urethral tissues for a distance of approximately one centimeter The scarred strictured area is excised Three equi distant incisions are made through the entire urethral wall at approximately 60° angles extending in 5 to 7 millimeters from the meatus To control the tissue 0000 dermalon suture on atraumatic needles is used as stay sutures Three small V shaped flaps of skin are cut at 60° to the tangent of the circular skin incision and elevated for incorporation into the circumference of the urethra The flaps are transposed and the apex of each skin V is sutured to the lowest point of one of the urethral incisions The apex of each mucosal V is

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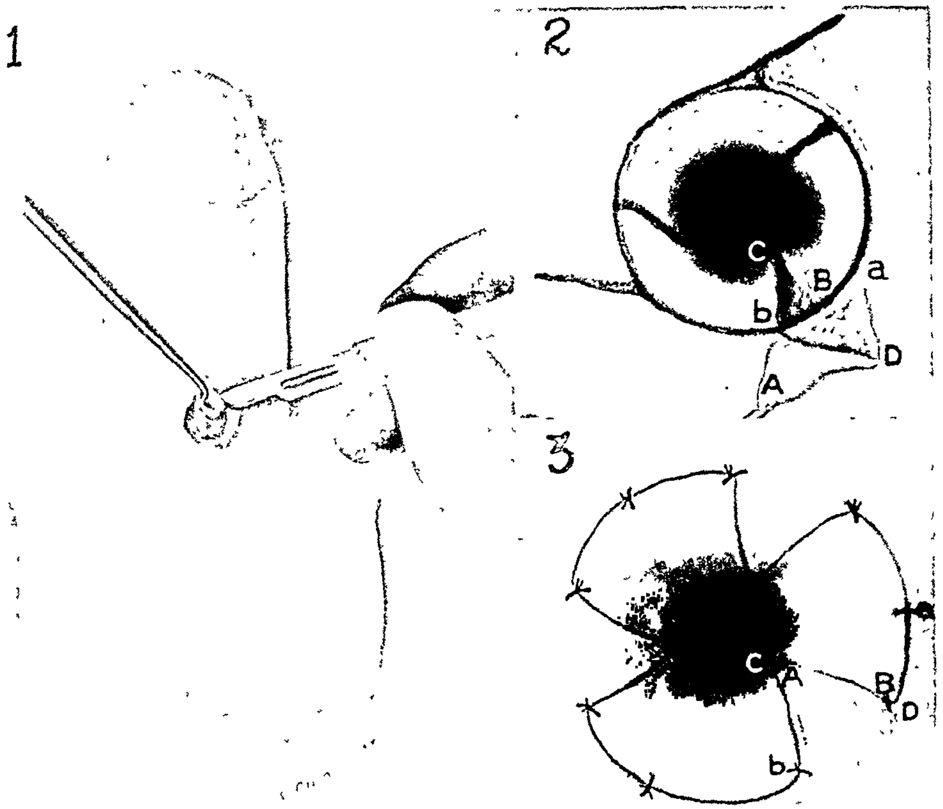

FIG. 1

sutured into the appropriate skin incision. The skin and mucous membrane margins are carefully approximated with 00000 dermalon sutures on an atraumatic needle. Fine mesh vaseline gauze is carefully placed into the urethral opening and an outer dressing of gauze and elastoplast is applied. The dressing is not disturbed until the sutures are removed on the sixth postoperative day. The perineal or suprapubic catheter is removed on the tenth or twelfth postoperative day.

The Z-plastic procedure in this instance increases the diameter of the urethrocutaneous meatus and gives a zig-zag line of closure of skin to urethral mucosa which prevents subsequent circular contracture.

CASE REPORTS

Case 1.—E. McG was a 4 year old white boy admitted to the University Hospital in January 1952. He had been circumcised at the age of 6 months. The physical examination was negative except for penile hypospadias with associated chordee. On January 22 a first stage repair was carried out with some difficulty due to the absence of a prepuce and extension of fibrous bands beneath the distal urethra. This necessitated a more extensive dissection about the urethra than is usually necessary. An excellent result was obtained and he was discharged on the tenth postoperative day. Five weeks following his discharge from the hospital he was readmitted with a one week history of dysuria, suprapubic pain, difficulty initiating urination, and a poor urinary stream. Physical examination revealed generalized cellulitis of the external genitalia with the height of reaction about the urethral meatus. On March 10, 1952 a permanent type perineal urethrostomy was done followed by rapid improvement of the cellulitis. He was re-admitted in July 1952 for consideration of a second stage repair but was found to have a meatal urethral stricture which accepted only a 6F filiform. A wide meatotomy was done on July 4, 1952 at which time a 16F bougie could be introduced with no difficulty. Following his discharge from the hospital he was seen several times in the out-patient department and despite repeated dilatations the urethral meatus was found to be only 8F in caliber. He was again admitted to the hospital in November and on November 10, 1952 the Z type plastic procedure described was carried out with excellent results.

Case 2.— G. C. was a 5 year old white boy admitted to the University Hospital in March 1952. Past history was negative. Although of small stature, physical examination was negative except for the external genitalia. The scrotum was extremely small with bilateral cryptorchidism. Penile hypospadias was present with chordee. On March 13, 1952 a first stage hypospadias repair was carried out with no difficulty and the postoperative course was uneventful. He was readmitted in July 1952 and on July 17, 1952 a Denis Browne urethroplasty was done, the urinary stream being diverted by the perineal route. The postoperative course was satisfactory until the fifth day when the perineal catheter came out and he voided through the newly formed urethra. A large fistula subsequently developed. One month following discharge from the hospital, he was admitted with a three day history of severe dysuria, suprapubic distress and dribbling urinary stream. Examination revealed a filiform urethral meatal stricture. The following day a suprapubic cystostomy and meatotomy were done with an uneventful postoperative course. At the time of discharge the urethra readily accepted a 14F bougie. He was not seen until January 1953 when he was admitted for consideration of closure of the urethrocutaneous fistula. On examination he was found to have recurrence of his meatal stricture which would not accept a 5F filiform. On January 14, 1953 a modified Z-plasty was performed with excellent results. Two months following repair a 16F bougie could be introduced into the urethra with ease.

DISCUSSION

The pitfalls associated with the repair of hypospadias are well known, especially those associated with the formation of fistula. However, we are inclined to believe that stricture of the urethra is a more common complication than one might assume and is equally as serious. It should be emphasized that proper care of the stricture is essential before further corrective surgical measures are carried out.

Two cases of meatal urethral stricture are presented both failing to respond to a wide meatotomy. The first resulted from a cellulitis of the external genitalia following a first stage repair. The second followed a breakdown of a Denis Browne urethroplasty. A good result was obtained in both cases employing a modified Z-plasty.

It would seem to us that a similar procedure would be of value in the correction of a ureterocutaneous stricture following transplantation of the ureters.

SUMMARY

Two cases of meatal urethral stricture following the repair of hypospadias are presented.

An operative technique employing a modified Z-plasty, which has been most successful in correcting this complication, is described.

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COMPLETE UNILATERAL WOLFFIAN DUCT AGENESIS WITH HOMOLATERAL CRYPTORCHISM, A CASE REPORT, ITS EXPLANATION AND TREATMENT, AND THE MECHANISM OF 'TESTICULAR DESCENT'

CLARK A WHITEHORN

The following example of complete unilateral wolffian duct agenesis with homolateral cryptorchism merits reporting for two reasons First, no report of a like situation can be found after a thorough search of the literature Secondly, the technique of retroperitoneal exploration is described and is considered mandatory to establish the diagnosis

CASE REPORT

K M , a 22 year old white airman, was admitted to the BAFB Hospital complaining of intermittent, dull, aching pain in the right lower quadrant of the abdomen of 2½ years' duration The distress became sharp and severe during any form of vigorous physical activity

The right testis had not been present within the scrotum since birth Otherwise there were no symptoms referable to the urinary tract

Family and past history add no further information

Positive physical findings were limited to the genital tract, tenderness to deep palpation, 4 cm above McBurney's point, was accompanied by mild muscle guarding without spasm No hernias were found

The penis was of adult size and presented a normal shaft, glans, and meatus The scrotum was grossly asymmetrical being without palpable contents on the right The cord could not be felt within the inguinal canal on this side The left scrotum and its entire contents were normal

Rectal examination revealed the right lateral lobe of the prostate to be small and atrophic The seminal vesicle and the vas deferens could not be outlined on the right The left lateral prostatic lobe, seminal vesicle, and vas deferens were normal in shape, size, and consistence

Urinalysis, hemogram, and serology were normal

Excretory urography demonstrated no evidence of a right renal shadow The left kidney appeared grossly hypertrophied Excretion of the dye was prompt at the end of 5 minutes The entire collecting system of the left kidney appeared normal A single ureter of normal configuration passed to a smooth, symmetrical bladder outline At no time could dye be visualized to arouse suspicion of the location of the right renal system

Subsequent cystoscopy disclosed a normal bladder but without evidence of a ureteral orifice on the right The right half of the trigone was flat The interureteral ridge ended in the midline The left trigone and ureteral orifice were normal A thorough search revealed no evidence of an ectopic right ureteral

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Read at annual meeting, Mid Atlantic Section, American Urological Association, Roanoke, Va , March 12–14, 1953 orifice. A 5F ureteral catheter, passed 29 cm. up the left ureter, encountered no obstruction. Retrograde pyelo-ureterograms added no further information.

A preoperative diagnosis constituted the following: agenesis, renal and ureteral, right; agenesis, seminal vesicle and prostate, right half; and right abdominal cryptorchism. The possibility of neoplasm of the cryptorchid testis was strongly considered because of the persistent right abdominal pain.

A complete right retroperitoneal exploration was performed. No contents were found within the inguinal canal. Very adequate exposure was obtained and the entire retroperitoneal space could easily be visualized from the region of the right renal fossa to the base of the bladder.

A complete agenesis of the right wolffian duct system was obvious. The right kidney, ureter, seminal vesicle, vas deferens, and epididymis were totally absent. The right testis was found in a most remarkable location. It was situated within Gerota's fascia in the right renal fossa. It derived its blood supply through a short, fatty pedicle originating from the aorta and vena cava. The ventral and inferior surfaces were densely adherent to the peritoneum and required sharp dissection. The pedicle was easily clamped and divided. The wound was closed in layers without drainage.

The postoperative course was uneventful. Wound healing was primary, and the patient enjoyed complete relief from his original distress.

The gross specimen consisted of a small testicle that had previously been opened. It measured 4½ cm. by 1 cm. The parenchyma of the testicle was light tan on sectioning. The capsule was thin and no attached epididymis or vas deferens was seen.

Examination of microscopic sections of the testis showed atrophy of the tubules. No spermatogenesis was seen in the seminiferous tubules. The tubules were lined mainly by primitive germ cells while other cells were undergoing degeneration in the lumina. The stroma of the testis was loose and Leydig cells were numerous. In the mediastinum only a few straight tubules were seen which were lined by columnar epithelium. No true rete testis was seen and there was no evidence of an epididymis. Diagnosis: Atrophic testis with absence of rete testis and epididymis.

EMBRYOLOGY

The upper urinary tract is derived from the embryologic mesodermal germ layer which develops 1) the pronephric duct, and 2) the nephrogenic cord. The lower urinary tract is entodermal in origin and will not be discussed.

PRONEPHRIC DUCT

The renal calyces, pelvis, ureter, trigone, epididymis, vas deferens, ampulla of the vas, and the seminal vesicles are derived from the primary excretory duct (primarily the pronephric duct which becomes the duct of the wolffian body).

The pronephric duct extends caudally to the cloaca. Its cranial end becomes the mesonephric ureter and is intimately related to the changes and growth of the mesonephros. The caudal end extends to the cloaca which it perforates and ultimately becomes the ejaculatory duct; the duct wall is drawn out to form that part of the urogenital sinus which later becomes the trigone. By a process of sacculation and lateral diverticulation, the ampulla of the vas and the seminal vesicles are formed from the vas deferens (caudal pronephric duct). In addition, near the terminal portion of the caudal end, the ureteric bud is given off, curves cranially and develops to form the ureter and primitive renal pelvis.

NEPHROGENIC CORD

The nephrogenic cord becomes the urogenital fold which later differentiates into 1) a mesonephros, 2) a gonad, 3) the metanephrogenic mesenchyme, and 4) Müller's duct.

The urogenital fold divides to form the lateral or mesonephric fold (the wolffian body) and an anteromesial fold, the genital fold.

1) The mesonephros undergoes degeneration from a cranial to caudal direction in two stages. During the first stage its tubules do not develop a communication with the primary excretory duct. However, before the second stage of degeneration, the surviving tubules develop glomeruli and do establish communication with the primary excretory duct, now known as the mesonephric ureter. The second stage of degeneration then occurs as follows: the epigenitalis (primitive epididymis) consists of the upper or genital portion of the degenerating mesonephric duct. The secretory portions completely degenerate and the remaining collecting portions enlarge, become thickened and convoluted, and end blindly in apposition with the rete blastima of the testis. These later become the collecting tubules of the epigenitalis and will communicate with the testicular rete tubules. The paragenitalis is the lower degenerating portion of the mesonephros. Its secretory portion degenerates completely. The remaining collecting tubules and primary excretory duct into which they enter unite to form one efferent duct which may persist in adult life as the paradidymis.

2) The genital fold consists of three portions. The upper end, the progonal portion, degenerates to form the suspensory ligament of the testis and will remain as the internal spermatic sheath. The midportion remains to develop as the gonad. The lower, or epigonal portion, becomes the ligamentum testis.

The two layered surface epithelium of the midportion forms the tunica albuginea. The many layered epithelium beneath forms the chordae testis. When the lumina develop in the chordae testis, the urogenital union occurs.

UROGENITAL UNION

This is an establishment of direct communication between the blind ends of the persisting mesonephric tubules of the epigenitalis with the lumina of the rete tubules of the testis to form ductuli efferentes testis. Thus patency and communication are established between the primitive testis and the epididymis.

3) The metanephrogenic cap accepts the ascending ureteral bud and its developing system of collecting tubules. Here it is to be noted only that the kidney is the final end product of this process.

4) Müller's duct is formed by an invagination of the coelom into the summit of the urogenital fold. The blind end grows downward independently of, but alongside, the primary excretory duct. The cranial end degenerates in the male to form the vagina masculina. Its degenerated cranial end persists as the appendix testis.

In the female the caudal ends fuse to form the uterovaginal canal and subsequently the vagina, cervix, and uterus. A portion also fuses with the urogenital sinus to become the hymen.

It is now seen that the original pronephric duct has formed the excretory passages for the entire urogenital system excluding the bladder and urethra. The cranial portion of the pronephric duct persists as the epididymis and joins the testis with patent communication in the urogenital union. The caudal portion of the pronephric duct persists as the vas deferens from which outpouchings form the ampulla of the vas and the seminal vesicles. It terminates as the ejaculatory duct. The ureteral bud is given off from the lower end of the pronephric duct, grows cranially, is engulfed by the metanephrogenic cap where the kidney is formed and persists as the adult ureter perforating the bladder; but it is still to remain in close approximation to the pronephric duct whose walls have been drawn out to form the trigone of the bladder.

MECHANISM OF 'TESTICULAR DESCENT'

In a 45 day embryo, 15 mm. in length, the gubernaculum consists of a continuous cord only 2 or 3 mm. long consisting of four different parts: 1) pars mesorchia (from the ligamentum testis in turn from the epigonal portion of the genital fold); 2) pars mesonephritica, consisting of two parts: a) the transmesonephric portion, and b) the mesonephric inguinal fold (both are from the mesonephric fold); 3) pars intermuscularis (from the abdominal musculature); and 4) the pars scrotalis (from the base of the genital tubercle).

The testis is attached to the abdominal wall in front by means of the inguinal fold of the mesonephros (part 2-b of the gubernaculum) before urogenital union occurs. As the abdomen enlarges and the embryo straightens out, the gubernaculum serves as an anchoring mechanism holding the testis anteriorly against the abdominal wall in the region of the internal inguinal ring.

Migration through the inguinal ring and canal is thought to be accomplished by embryonic cremasteric muscle action much in the same fashion as descensus occurs in certain of the *rodentia* at the period of sexual excitement. Final descent into the scrotum depends upon anatomical development of the scrotum and a patent third inguinal ring.

CASE EXPLANATION

This is an example of complete pronephric, or wolffian duct, agenesis with abdominal cryptorchism. Congenital absence of the pronephric duct accounts for the absence of the vas deferens, seminal vesicle, ureter, and trigone. Failure to find any structure resembling kidney and epididymis is best explained on the basis of complete degeneration of the metanephrogenic cap and the mesonephros when the necessary stimulus from the absent pronephric duct did not arrive.

The testicle did not "descend" because the gubernaculum was incomplete. Due to degeneration of the mesonephros, the inguinal mesonephric fold *could not* be formed and, therefore, the testis *could not* be anchored to the abdominal wall. As the embryo lengthened and straightened the testis *remained* in the region of the renal fossa.

TREATMENT

It is not the purpose of this paper to discuss the various surgical procedures employed in the treatment of cryptorchism nor the age at which surgical intervention should be performed.

The cryptorchid testis and the vas deferens are retroperitoneal in location. A retroperitoneal approach should then be employed in such a fashion that complete exploration may be afforded from the region of the internal inguinal ring to the renal pedicle if necessary. The following procedure fulfills these requirements.

The initial incision begins over the upper one-third of the inguinal canal and is carried upwards towards the tip of the eleventh rib far enough to permit exploration of the inguinal canal after the aponeurosis of the external oblique is opened. The internal oblique and transversus abdominis muscles are then transected down to the retroperitoneal fascia which is easily separated from the abdominal wall by blunt dissection. If the testis does not present itself in the inguinal region, the incision is then carried upwards through the skin and all muscle layers to the tip of the eleventh rib. The peritoneum with the retroperitoneal fascia is rolled from the lateral and posterior abdominal walls by blunt dissection. Rotating the operating table to the opposite side gives very adequate visualization from the renal pedicle to the base of the bladder. Normally the internal spermatic vessels, the vas deferens, and the ureter may be seen through the retroperitoneal fascia which must be opened to expose them.

The cryptorchid testis may then be adequately dealt with regardless of its position. Management of the testis itself will be dictated by the individual circumstances encountered. Orchiectomy may be required as in this case. A first stage Torek procedure may be completed or performed in stages in the interval fashion of Cabot after the internal spermatic vessels and the vas deferens have been freed and preserved. Creating a new opening through the transversalis and internal oblique muscles medial to the deep epigastric vessels will shorten the path of the internal spermatic vessels into the scrotum, when the cord is too short, by eliminating the long course through the inguinal canal. The wound is closed in layers without drainage.

It is to be emphasized that no matter where the testis is situated, preservation of the internal spermatic artery is a primary requisite if spermatogenesis is to be expected. Wangensteen and Griffiths have both shown without question that spermatogenesis ceases after ligation of the internal spermatic artery.

DISCUSSION

The case herein cited represents an example of complete unilateral wolffian (pronephric) system agenesis with homolateral cryptorchism. A detailed review of the literature presents no other similar case. Special interest is merited because the cryptorchid testis was found within Gerota's fascia, held in the upper abdomen by the internal spermatic sheath because of failure of development of the gubernaculum testis.

Only one report is found in the literature disclosing the presence of the testis at the renal hilum. Lowsley and Curtis explored transperitoneally for bilateral cryptorchism and finally discovered the right testis at the level of the renal hilum only after following the vas deferens upwards from its terminus in the ampulla of the vas. Had not the vas deferens with its upward retroperitoneal extension been present, it is unlikely that the true location of the testis would have been found.

Other authors may have discouraged the finding of such cases by continuing to quote Felix who in 1917 wrote, "Undescended testes do not lie in the region of the kidney as was previously thought. A testis, if present in the abdomen, will be found in the region of the internal ring and thus easily should be located when the abdomen is opened."

Felix was probably led to this conclusion by noting that the testis is attached to the anterior abdominal wall by the mesonephric inguinal fold. However, remembering that the embryonic gubernaculum is a structure composed of four portions having separate origins, then Felix's statement holds true only if the first two portions are intact. If the mesonephric inguinal fold undergoes degeneration, the testis cannot be anchored to the abdominal wall and therefore the cryptorchid testis will *not* be found in the region of the internal inguinal ring. In reality, an abdominal cryptorchid testis may be one which was actually *migrated* in a cranial direction instead of remaining fixed to the anterior abdominal wall as does the normal testis prior to its descent through the inguinal canal into the scrotum.

The same line of reasoning explains other aberrant locations of the cryptorchid testis. Should the pars scrotalis of the gubernaculum be absent, the testis will remain in the region of the external inguinal ring. An absent pars intermuscularis will leave the testis at or just inside the internal inguinal ring. A missing mesonephric inguinal fold will find the testis between the internal inguinal ring and the region of the renal pedicle. Failure of the pars mesorchia and the transmesonephric portions of the gubernaculum would leave the testis in a similar position. Failure of the pars mesorchia associated with complete urogenital separation (failure of urogenital union) would allow the testis to remain in its high position, but by virtue of a transmesonephric attachment, the epididymis and the vas deferens would then be found along the pathway of normal "testicular descent".

Such an attachment of the gubernaculum to the vas deferens and epididymis was noted by Curling in 1840 who wrote, ". . . the gubernaculum is connected above with the inferior extremity of the testicle, and to the lower end of the epididymis and commencement of the vas deferens".

Therefore, if only the vas deferens and the epididymis are found on inguinal exploration, the possibility of finding a much higher intra-abdominal testis is not excluded. The above reasoning also explains the statement of Dean, Major and Ottenheimer: "In all recorded instances of separation of the testis and epididymis, the testis has always been undescended, located cephaled to the epididymis. . . . No instances were found in which the testis descended into the scrotum without its accompanying epididymis, although the reverse is true."

It is now apparent that complete retroperitoneal exploration to the level of the renal pedicle is mandatory when a cryptorchid testis is not found near the internal inguinal ring. A diagnosis of monorchism is not valid unless such an exploration has been performed.

Routine radical (complete) retroperitoneal exploration is suggested in all cases where the testis is not found at the internal inguinal ring.

SUMMARY AND CONCLUSIONS

A case of complete unilateral wolffian duct agenesis with homolateral abdominal cryptorchism has been presented. No similar case has been found in a careful search of the literature.

Using a technique similar to that of radical retroperitoneal lymph node dissection, the testis was found within Gerota's fascia where the absent right kidney should have been. The right kidney, ureter, trigone, epididymis, vas deferens, and seminal vesicle were absent.

A review of the embryology of the upper urinary and genital systems is presented. The mechanism of "testicular descent" is discussed.

"Testicular descent" depends upon the integrity of a gubernaculum composed of four separate portions, each having a different source of origin. The testis can descend no lower than the most distal segment of the continuous gubernaculum.

The epididymis and the vas deferens may descend alone without the testis in cases of failure of urogenital union. Finding only the first two structures below the internal inguinal rings does not preclude finding an abdominal testis as high as the renal pedicle.

The technique of complete retroperitoneal exploration is mandatory when the cryptorchid testis is not found at the internal inguinal ring. The retroperitoneal exposure for orchiopexy is recommended so that the internal spermatic vessels may be freed under vision. Preservation of the internal spermatic vessels is essential if spermatogenesis is to ensue.

I should like to express my gratitude to Dr. Lloyd G. Lewis for his inspiration, counsel, and guidance in the preparation of this paper.

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TESTICULAR DYSGENESIS AS AN ETIOLOGIC FACTOR IN CRYPTORCHIDISM

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It has long been conjectured that inherent disorders of the testis may be related to or responsible for maldescent. The pioneer observations of John Hunter (1728-1793) led him to suspect that congenital testicular imperfection prevents descent and interferes with normal function.[1] In 1910 Bland-Sutton[2] revived the concept that a testis is retained because it is imperfect. Subsequently, other workers[3, 4, 5, 6] subscribed to the belief that testicular "infantilism", "undevelopment" or "hypoplasia" may play a role in the etiology of cryptorchidism. Nelson[7] has recently stated the view that in certain cases undescended testes may be an expression of defective development. The indefinite state of our knowledge of this problem is reflected in the fact that various urological textbooks[8-11] and review articles[12, 13] fail to mention it.

In an effort to shed further light on the relationship between testicular maldevelopment and maldescent, a series of cryptorchid glands was subjected to systematic histologic analysis. The purpose of the present communication is to record the results of this investigation in which microscopic evidence of testicular dysgenesis was encountered with significant frequency. Since these findings were not observed in a control group of normal scrotal testes from corresponding age periods it is felt that they may represent factors of etiologic importance in some cases of cryptorchidism.

MATERIAL AND METHOD

Table 1 enumerates the pertinent data of 42 patients whose imperfectly descended gonads were studied. The age range is from prematurity (7 months) to 78 years. The testicular specimens were obtained at necropsy in 7 cases. In 35 patients fresh testicular tissue was provided surgically, 6 by biopsy and 29 by ablation.

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TABLE 1. *Pertinent data on 42 patients with undescended gonads*

Case No.	Age	Side*	Size† (cm.)	Location	Method of Obtaining Specimen	Evidence of Dysgenesis	Remarks
1	Premature (7 mos.)	R	0.9	Canal	Autopsy		
2	2 days	R	0.9	Abdomen	"		Multiple congenital anomalies
3	2 mos.	rL	—	Canal	Biopsy		Pseudohermaphrodite
4	4 "	Rl	1	Abdomen (R) Canal (L)	Autopsy		Multiple congenital anomalies
5	6 "	Rl	1.1	Abdomen	"		Multiple congenital anomalies
6	7 "	Rl	1.3	Abdomen	"		Congenital encephalopathy
7	7 yrs.	Rl	1	Canal	"		
8	10 "	L	1.1	Canal (mid)	"		
9	10 "	L	1.3	Canal	Ablation	Germinal aplasia	
10	12 "	R	2	Abdomen	"	Immature tubules (majority)	
11	13 "	Rl	1.5	Abdomen	Biopsy	Immature tubules (about 50 per cent)	Shortness of stature
12	13 "	L	—	Canal (mid)	"		
13	13 "	RL	1 x 0.7 x 0.5 (R) 1.5 x 1.2 x 0.8 (L)	Abdomen	Ablation	Germinal aplasia. Immature tubules (rare small foci)	Hermaphrodite
14	15 "	L	—	Canal (low)	Biopsy		
15	17 "	L	2.5 x 1.5 x 1	Abdomen	Ablation	Immature tubules (many small foci)	
16	18 "	L	3 x 2.5 x 2	Canal	"	Immature tubules (single large focus)	
17	21 "	R	3.5 x 2.5 x 2.5	Canal	"		
18	23 "	Rl	0.5	Canal (high)	"	Absence of spermatogonia, Sertoli and Leydig cells	Prepuberal hypogonadism
19	27 "	Rl	"normal"	Outside ext. ring	Biopsy		Pseudohermaphrodite Dwarfism
20	28 "	L	2 x 1	Canal	Ablation	Immature tubules (few small foci)	
21	28 "	R	"small"	Canal	"	Immature tubules (about 40 per cent)	
22	29 "	R	1.8	Canal	"		
23	30 "	L	"small"	Canal	"	Immature tubules (many small foci)	
24	30 "	R	2.5	Abdomen	"	Immature tubules (occasional small foci)	
25	30 "	R	3	Outside ext. ring	"		
26	30 "	R	Tumor 140 g.	Abdomen	"	Immature tubules (rare large compact groups)	Seminoma
27	31 "	R	3 x 2 x 1.5	Canal (high)	"	Immature tubules (many small foci)	
28	33 "	L	"fair"	Abdomen	"		
29	35 "	R	Tumor 9 x 7 x 6	Outside ext. ring	"		Malignant teratoma
30	36 "	R	4 x 2 x 1	Canal	"	Immature tubules (many small foci)	
31	36 "	rL	"fair"	Canal	Biopsy		

TABLE I.—*Continued*

Case No.	Age	Side*	Size† (cm.)	Location	Method of Obtaining Specimen	Evidence of Dysgenesis	Remarks
32	38 yrs.	L	"atrophic"	Canal (low)	Ablation	Immature tubules (few small foci)	
33	39 "	R	2.7	Abdomen	"	Immature tubules (about 20 per cent)	Seminoma (early)
34	39 "	L	4.5 x 3 x 2.5	Abdomen	"		
35	41 "	R	3 x 0.5	Abdomen	"		
36	42 "	R	3.5 x 2.5 x 1	Canal (low)	"		
37	42 "	R	3.5 x 2 x 2	Canal	"		
38	48 "	R	3.5 x 1.5 x 1.2	Canal	"	Immature tubules (single small focus)	
39	50 "	R	3 x 2.5 x 1.5	Canal (high)	"		
40	*52* "	*R*	*2.5*	*Abdomen*	"	*Immature tubules* (few small foci)	
41	52 "	R	3.5 x 3 x 1.8	Outside ext. ring	"		
42	78 "	R	2.9 x 2 x 1.9	Canal (low)	"		

* Where bilateral cryptorchidism existed the examined gonad is indicated by the capital letter.

† In the absence of exact measurements the available surgical or pathological description is given.

The majority of the patients showed no evidence of constitutional or endocrine disease. Associated congenital anomalies were present in 4 infants (cases 2, 4, 5 and 6). Two individuals aged 2 months and 27 years (cases 3 and 19) were male pseudohermaphrodites. A 13 year old patient (case 13) was a true hermaphrodite. The gonads are included in the present study because they were composed almost entirely of testicular tissue. Prepuberal hypogonadism was present in a 23 year old man (case 18). Involvement by malignant tumor occurred in 3 instances (cases 26, 29 and 33).

A group of 64 normal scrotal testes derived from 59 patients served as controls. These ranged in age from prematurity (5½ months) to 59 years. Testicular tissue from 32 patients up to the age of 17 years was obtained at autopsy. The remainder was provided by open biopsy or ablation. Specimens which showed gross or microscopic evidence of disease, atrophy or fibrosis were excluded. Despite the limitations imposed on precise cytological analysis by postmortem examination, especially in persons succumbing to a fatal illness, the material obtained from this source compared favorably with the surgical preparations for the purposes of this investigation. The testicular specimens were fixed in 10 per cent formaldehyde in most of the cases. A few of those obtained by biopsy were fixed in Bouin's solution.

RESULTS

After the prepuberal period. Areas of seminiferous tubules of a prepuberal type (containing undifferentiated rather than Sertoli cells) were identified in the undescended gonads of 14 out of 28 individuals aged 17 years or more and in 3 out of 5 patients ranging between 12 and 15 years of age.

As observed in 17 cryptorchid patients beyond the prepuberal era, the number and distribution of immature tubules displayed considerable variation. In the majority of cases they were found singly or in small groups consisting of 3 to 20 tubules lying closely together (fig. 1, *A*). Although the immature tubules were always subnormal in size for the age of the individual their actual diameters exhibited considerable variation from case to case.

Varying degrees of tubular immaturity were manifested. Marked immaturity was characterized by smaller solid tubules. Their cell population was usually quite dense causing the tubules to appear filled with nuclei (fig. 1, *B*). Somewhat less immaturity was manifested by tubules which tended to be larger, slightly tortuous and to contain relatively fewer cells. The latter were usually present in layers of one to three cell thickness around the periphery of the tubule often with their long axes perpendicular to the basement membrane. Gradual lessening in the degree of immaturity was characterized by further increase in tubular diameter and tortuosity and progressive changes in the undifferentiated nuclei. In addition to an overall increase in size, the nuclei were more often oval than round. However, they were occasionally quite narrow and elongated with a pronounced tendency to be arranged at right angles to the enveloping basement membrane. This created, at times, a striking palisade-effect.

The focal grouping of immature tubules presented a distinctive variation in 3 patients (cases 20, 26, 30). In contrast with the other cases showing discrete circular or oval cross sections of tubules lying singly or in islands, the tubules in these cases were closely set in compact, sharply circumscribed units with a nodular or lobulated appearance (fig. 2). The nuclei of the undifferentiated cells were numerous and exhibited considerable pleomorphism. Palisading of narrow elongated nuclei was especially conspicuous in the narrower elongated tubules.

The presence of spermatogonia could be established with certainty in the immature tubules in but one patient, a 12 year old boy (case 10). In no instance were definite lumens found in immature tubules.

In approximately one-half of the cases one or more immature tubules contained eosinophilic, colloid-like bodies (fig. 2, *A*). A unique finding was present in the immature tubules of case 26 (fig. 2, *B*). Most of this intra-abdominal testis was destroyed by seminoma. In the grossly and microscopically uninvolved portion near the surface there were several groups of nodular units of compact immature tubules. Occupying the central portion of many of these tubules were large oval, fairly homogeneous masses. Although the partially eosinophilic character of these masses created a superficial resemblance to the colloid-like bodies they were not identical. In addition to being larger and exerting pressure on adjacent cells, they had the morphologic and staining characteristics of calcium.

An outstanding feature of the immature tubules was the comparative freedom of their basement membranes from significant fibrotic thickening. This was in marked contrast to the sclerosis of mature tubules in the same section of most adult cryptorchid testes. Sharing this partial immunity to the deleterious effects of cryptorchidism were the undifferentiated cells of the immature tubules. In general their nuclear integrity was well preserved. This was in decided contrast to the findings in most mature tubules. In addition to progressive fibrosis the

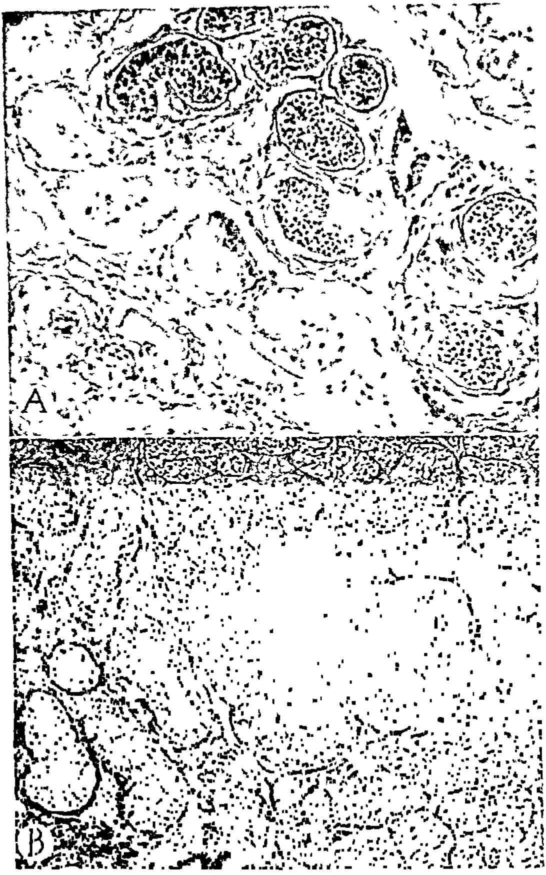

FIG. 1. *A*, nest of immature seminiferous tubules in intra-abdominal testis of a 52 year old man (case 40). Marked immaturity is characterized by very small solid tubules densely packed with undifferentiated cells Spermatogonia are absent and there is negligible thickening of basement membranes. Below are a few markedly fibrotic and hyalinized tubules showing no or little residual lumen. (× 200)

B, Large number of closely set immature tubules in the canalicular testis of a 28 year old man (case 21). Tubules are small, solid and densely packed with undifferentiated cells having ovoid or elongated nuclei. Their basement membranes are slightly thickened. Immediately adjacent on left is a group of tubules which had previously matured to extent that they contain differentiated Sertoli cells and spermatogonia. These tubules are considerably larger, have lumens, contain relatively fewer cells and show moderate fibrosis of basement membranes and peritubular connective tissue. Leydig cells are conspicuously grouped in dense collagenous intertubular tissue. Latter tends to penetrate adjacent mass of immature tubules. (× 100)

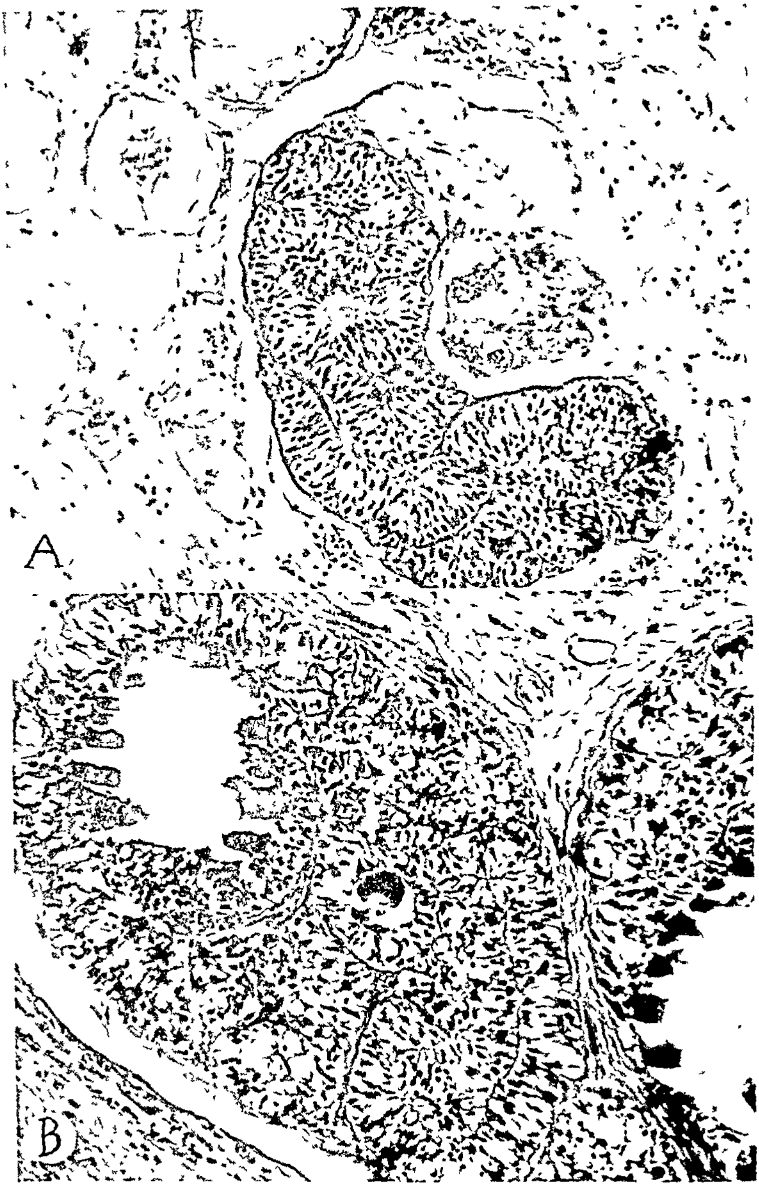

FIG. 2. *A*, sharply circumscribed unit of compact immature tubules in inguinal testis of a 36 year old man (case 30). Basement membranes of individual tubules are not always distinct. Intratubular epithelial cells are numerous and exclusively of undifferentiated type. They exhibit considerable pleomorphism and occasional palisading. Central colloid-like bodies are present. Adjacent tubules show marked fibrosis and hyalinization. (× 200)

B, sharply circumscribed units of compact immature tubules in intra-abdominal testis of a 30 year old man (case 26). Most of this gonad was destroyed by seminoma but this section is from uninvolved portion near surface. Large calcific concretions have formed in several tubules causing pressure on adjacent undifferentiated cells. Fragmentation is an artefact. Spermatogonia cannot be identified with certainty. Basement membranes of component tubules are indistinct in some places and slightly thickened in others. (× 200) latter usually showed a significant decrease in cell population and residual Sertoli cells were often in a state of degeneration.

Prepuberal period. The retained testicles of 7 boys ranging in age from prematurity to 7 years showed little, if any, deviation from the histologic pattern of normal scrotal glands of corresponding ages. In two boys of late prepuberal age, however, notable differences were encountered.

The canalicular testis of a 10 year old boy (case 8) was approximately two-thirds the size of its scrotal mate. Although there was histologic evidence of early maturation in both testicles this was decidedly retarded in the retained gonad where spermatogonia were also less numerous.

In another 10 year old boy (case 9) the tubules of the inguinal testis were completely lacking in spermatogonia. The tubules were tightly packed with numerous undifferentiated cells, some of which were enlarging. However, none showed plasmosomes indicative of Sertoli cell differentiation.

DISCUSSION

The recognition of testicular dysgenesis depends upon two major considerations. Firstly, seminiferous tubules of the prepuberal type (containing undifferentiated rather than Sertoli cells) are not encountered in the normal scrotal testicle beyond the prepuberal age. Their presence in the gonad of an adult is, therefore, an indication of immaturity. In the absence of a recognizable constitutional, metabolic or endocrine disorder this finding denotes an inherent developmental defect of a congenital nature. This conclusion is equally valid for the cryptorchid testis where tubular immaturity is readily distinguishable from tubular regression, atrophy and fibrosis. The latter are degenerative changes secondary to maldescent. Although it is difficult to prove that tubular immaturity in the undescended testis is not a consequence of cryptorchidism *per se* the weight of the evidence suggests that the converse is true.

Equally essential for the identification of certain types of testicular dysgenesis is the verified absence of cytological components such as spermatogonia, Sertoli or Leydig cells. This must not be the result of postnatal local or systemic noxious influences. Furthermore, the age of the patient with respect to puberty is of utmost importance. *Before puberty*, spermatogonia are present in the tubules of the normal scrotal as well as the cryptorchid testis. Their total absence in normally or abnormally situated gonads in this age period is pathological and, therefore, congenital in origin. *After the completion of puberty*, Sertoli and Leydig cells are found in scrotal and retained glands although their number and distribution may be disturbed in the latter. The partial or complete absence of Sertoli cells or the total absence of Leydig cells from the adult testis (under the conditions stated above) is indicative of an inherent congenital defect.

In the present study of cryptorchid testes three varieties of testicular dysgenesis were recognizable histologically. In descending order of frequency these were:

1) Various degrees of tubular immaturity occurring after the prepuberal age.
2) Total absence of spermatogonia just before and during the puberal period.
3) Complete absence of spermatogonia, Sertoli and Leydig cells in an adult.

There was no definite correlation between the type or extent of defective gonadogenesis and the degree of maldescent. Dysgenetic testicular lesions were approximately evenly divided among abdominal and canalicular glands.

Seminiferous tubular immaturity. This was the most frequent type of congenital testicular defect encountered in this series. Seminal tubules of a prepuberal type were identified in the retained gonads in 17 out of 33 individuals beyond the age of 10 years. The high incidence of this type of tubular immaturity and its absence from a control group of 39 normal scrotal testes from 34 patients of corresponding ages emphasize the relationship between testicular maldevelopment and maldescent.

The presence of immature seminiferous tubules in the adult cryptorchid testis has been mentioned previously by Uffreduzzi[3] and by Sniffen.[14] Immature tubules have also been described[15] in the descended testes of certain men with the Klinefelter-Reifenstein-Albright syndrome[16] and in other forms of hypogonadism.[17] These observations indicate that a testis may descend into the scrotum despite its congenital defectiveness.

The finding of colloid-like bodies centrally situated in some immature tubules is consistent with their prepuberal character. These structures are apparently identical with those first described in the tubules of prepuberal normal scrotal testes by Blumensaat.[18] The significance of the intratubular calcific concretions in case 26 remains unclear. They seem to correspond to the "stones" first reported in postpuberal testicular tubules by Oiye.[19]

It is particularly noteworthy that the immature tubules appear to exhibit considerable resistance to the sclerosing and destructive effects of cryptorchidism. This contrasts sharply with the fibrotic obliteration and epithelial degeneration of tubules which had previously matured. The reason for this relative immunity is not clear but the fact itself is important with respect to the cause of the immaturity. Tubules, like other body structures, fail to develop because they are inherently incompetent or because they are inhibited or unstimulated. The injurious effects of cryptorchidism on the prepuberal testis are meager and difficult to recognize while those seen after puberty are numerous and conspicuous. It is, therefore, evident that the deleterious effects occur principally *after* the tubules have matured. For this reason it is most unlikely that cryptorchidism inhibits maturation of prepuberal tubules to the extent of preventing transformation of their undifferentiated cells into Sertoli cells. If this were not true one would expect at least as much destruction of immature as of mature tubules. In the absence of other local or constitutional factors the conclusion is inescapable that tubular immaturity in the postpuberal testis is due to an intrinsic congenital defect.

Further support to this concept is given by the great paucity of germinal cells within the immature seminal tubules. Here, again, this observation cannot be ascribed to the injurious effects of cryptorchidism since residual spermatogonia were readily found elsewhere in the same sections in sclerotic tubules which had previously matured. It seems reasonable to conclude that the absence of germinal cells in these immature tubules is additional evidence of their primordial defectiveness.

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The sharply circumscribed units of compact immature tubules noted in cases 20, 26 and 30 merit special comment. Under low-power magnification the microscopic appearance of these nodular structures bears a striking resemblance to that of the *testicular adenomas* described and illustrated by Pick[20] and Lecène and Chevassu[21] in undescended testes. However, it is evident that these 2 types of nodular formations in cryptorchid testes are unrelated.

The apparent similarity of the nodular lesions in the present cases to new-growth formation is underscored by a report in the literature.[22] In this instance it appears that characteristic microscopic foci of immature tubules were interpreted as early adenocarcinoma in retained testes. In another report, Scully and Parham[23] describe and illustrate a lesion in a cryptorchid testis as a testicular adenoma, with the reservation that it is probably not a true tumor. In this instance, too, the lesion appears to be a characteristic circumscribed focus of immature tubules.

Absence of specific cytological components. Additional manifestations of testicular dysgenesis were encountered in 3 patients whose undescended gonads were completely lacking in one or more types of specific cellular elements.

Spermatogonia could not be identified in any of the tubules of the inguinal testis of a 10 year old boy (case 9). While it is not uncommon to find a diminished number of germ cells in cryptorchid testes in the late prepuberal or early adolescent era,[7, 24] their complete disappearance as a result of malposition is not definitely known to occur before late adolescence. At the age of 10 years, therefore, it is most unlikely that the absence of spermatogonia is attributable to cryptorchidism per se. Since there was no history or evidence of local or systemic disease which might destroy germinal cells, their absence in this case is presumably due to a congenital defect. This type of lesion was first described in otherwise normal scrotal testes by Engle[25] who later[26] termed it *germinal aplasia.* Engle[27] and others[28, 29, 30] believe it to be of congenital origin when known germ cell antagonists can be excluded.

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Absence of spermatogonia was also established in both abdominal gonads of a 13 year old hermaphrodite (case 13). The sex glands of this patient were included in the study because they consisted preponderantly of testicular tissue. However, a few scattered microscopic foci of typical ovarian stroma lacking in ova or follicles indicate that the gonads are actually ovotestes. The absence of spermatogonia is regarded as due to germinal aplasia for the same reasons that applied in the previous case. An inherent defect in gonadogenesis readily explains the multiplicity of congenital lesions in this patient (germinal aplasia, focal tubular immaturity and ovarian stroma).

Absence of spermatogonia, Sertoli and Leydig cells in a 23 year old man with prepuberal hypogonadism (case 18) indicated the most marked degree of testicular dysgenesis encountered in this series. This patient has been described in detail elsewhere.[31]

SUMMARY AND CONCLUSIONS

The incompletely descended gonads of 42 patients were studied in an effort to elucidate the relationship between maldevelopment and maldescent of the testicle. Special attention was devoted to the detection of histologic evidence of defective gonadogenesis (testicular dysgenesis).

Three varieties of testicular dysgenesis were encountered. The most frequent type was seminiferous tubular immaturity occurring after the prepuberal age. This was noted in approximately one-half of the cases. Much less frequent was another type of congenital lesion characterized by complete absence of spermatogonia (germinal aplasia) just before and during the puberal period. The least frequent and most profound developmental defect was found in the rudimentary testis of an hypogonadal adult. In this instance germinal cells, Sertoli and Leydig cells were absent.

The high incidence of dysgenetic testicular lesions in this series of undescended testes supports the view that testicular imperfection is of etiologic significance in some cases of cryptorchidism.

I am grateful to Dr. Sadao Otani who kindly placed the microscopic sections at my disposal.

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REPORT OF CASE OF DUPLICATION OF LEFT UNDESCENDED TESTICLE

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The multiplicity of congenital defects even within one system is well known, but the duplication of an undescended testicle is rare enough to merit the report of any case showing this anomaly. Parke Smith et al.[1] (1950) in an excellent review reports the incident of proven polyorchism as reported but nineteen times in the literature. Campbell[2] says the condition has been found most often on the left side. A biposy is necessary to differentiate all conditions that may be confused with a supernumerary testicle, some of these being spermatoceles, small encysted hydroceles, splenic rests and adrenal rests. The following case of left cryptorchism with polyorchism is reported.

F. R., a white boy, aged 9, King's Daughters Hospital No. 51764, was first seen in the office in July 1953 with complaint of a left undescended testicle. Physical examination revealed the absence of a left testicle and epididymis in the scrotum with no cord structure found leading out of the external ring. A mass 2 by 1 cm. could be palpated in left inguinal canal. The right testicle was of normal size, position, and motility. The rest of the physical examination was negative. The boy was well developed with a normal stature for his sex and age. A course of Antuitrin S (Parke-Davis) 500 units biweekly was started. After receiving 3,500 units the boy had marked enlargement of the penis, sparse pubic hair being present and enlargement and tenderness of the mass in the left inguinal region. This therapy was discontinued and exploration carried out 10 days later. Examination of the urinary tract by excretory urography and cystoscopy failed to reveal further anomalies. Laboratory studies of blood and urine were normal.

Exploration through a left hernia approach of the left inguinal region was done August 31, 1953. The external ring was located and no cord structures were present. The aponeurosis of the external oblique over the inguinal canal was split and two definite masses, some 3 cm. apart, were present. Further dissection showed no connection between these two and the vas deferens entered into an epididymis and the lower mass, but most of the vessels stopped at the superior mass. A biopsy of each mass was taken and frozen section revealed testicular tissue to be present in each mass, but the lowermost one showed much fibrosis and atrophic tubules. This was supplemented by a later permanent section. The mass was also much harder than normal testicular tissue. It was the opinion of the pathologist that this mass was almost useless as far as functioning tissue was concerned. Therefore, this lower mass was excised, the vas deferens being tied off above the epididymis. The numerous adhesions of the vessels of the superior testicle were freed and adequate length obtained so that the testicle could be

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Accepted for [illegible], 1954.

[1] Smith, P. [illegible] J Urol., 64: 515, 1950.

[2] Campbell, [illegible]: Clinical Pediatric Urology. Philadelphia: W. B. Saunders Co., 1951, p. 323.

brought down to its normal position in the scrotum without undue stress on these vessels. A hernia was repaired at this time by dissecting the sac free, excising the excess portion and closing the neck with a chromic 0 purse string suture. A Torek repair with suture of the testicle to the fascia lata of the inner thigh was the method of choice of repair. The hernia repair was completed by means of the Bassini method. After 11 weeks a second stage Torek was done and the testicle was relocated in its normal position in the scrotum without evidence of any retraction.

DISCUSSION

Excision of the fibrotic testicle in this case beyond doubt made the patient sterile on that side as no vas deferens connects with the salvaged testicle, but with a testicle as fibrotic as this, severe doubt of any future production of sperm would be present. The healthy testicle was transplanted to the scrotum only for hormone production and cosmetic appearance, as well as getting it in a position so that it may be watched for any possible future development of a malignancy. The multiplicity of congenital deformities is demonstrated in this case.

SUMMARY AND CONCLUSIONS

A histologically proven case of polyorchism is reported. This was one of two congenital deformities in the genito-urinary system, the other being cryptorchism.

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THE ADRENAL RESPONSE TO IRRADIATION ON PATIENTS WITH TESTICULAR TUMORS

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Recent medical progress has resulted in a better understanding of the physiology of the adrenal glands. Alterations in adrenocortical function can now be determined with reasonable accuracy.[1] One of the factors or stimuli that may cause a change in the cortex of these glands is the use of the roentgen ray. Lawrence[2] demonstrated alterations in the adrenal glands of dogs after total body irradiation. That external irradiation, applied therapeutically, can have an effect on the adrenal glands, has been demonstrated by Porter.[3]

In order to study further these changes in adrenocortical activity, patients receiving large doses of external irradiation for the treatment of malignant disease of the testes were selected for investigation.

METHODS

Ten patients, 20 to 40 years of age, who had varying types of testicular tumors, were selected. Each individual was evaluated before the beginning of the study; only volunteers were used. For the majority of patients, it was possible to obtain a 24-hour urine specimen for the steroid determination before excision of the diseased testis; in some of the patients, the testis was removed at another hospital. After surgical removal of the malignant tumor, a period of 4 to 6 days elapsed before the return of the pathologic report. For the patients who had the operation in other institutions, approximately the same amount of time elapsed before sections of the tumor could be studied. Three hundred roentgens were given in air daily, alternating front and back, 220 kv, 15 ma., filter 1/2 (0.5) cu., and 1 al., target skin distance 50 cm., with r/min 49.2 from the inguinal area progressively to the supraclavicular area. Therapy was given over a period averaging 65 to 70 days. This produced a skin dosage of approximately 3600 r to the inguinal and abdominal ports and 2400 to 3000 r to the chest and supraclavicular areas. The calculated penetrating total tumor dosage was between 2500 and 3000 r (fig. 1). During the period of treatment all patients were maintained on a high protein, carbohydrate and vitamin diet.

Laboratory studies included 24-hour urinary 17-ketosteroid and 11-oxycorticoid determinations, white blood count, hemoglobin, and total circulating eosinophile count. The 24-hour urinary 17-ketosteroids were determined daily

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* Present address: 99 Larchmont Road, Buffalo 14, N. Y.

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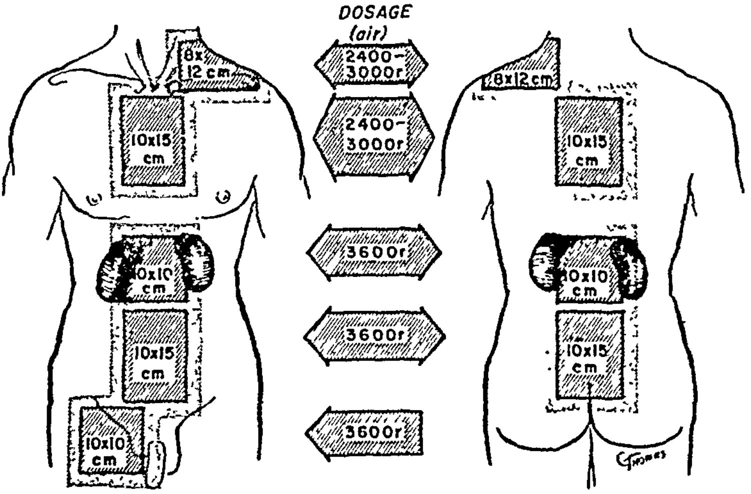

FIG. 1. Portals for routine radiation of testicular tumors

by the method described by Cahen.[4] The normal value for men between the ages of 20 to 40 years at this laboratory is 15 to 25 mg. per 24 hours. The 11-oxycorticoids were determined daily by the method described by Daughady.[5, 6] The normal value for a 24-hour urinary excretion is 1 to 3 mg. per 24 hours. The total circulating eosinophile counts were all taken at 8 a.m. and, on the days when ACTH was given, they were repeated at noon. The counts were done according to the methods described by Bonner,[7] and the results of the response were correlated with the work of Roche and co-workers.[8] Upon completion of each period, the urine was sent to the laboratory for total 17-ketosteroids and 11-oxycorticoid determinations. Hemoglobin, white blood cell count, and total eosinophile estimations were made three times a week. Approximately every tenth day, ACTH was given, intravenously or intramuscularly, in order to assess the adrenal response by changes in steroid excretion and eosinophile count. All of the studies were performed by specially designated laboratory personnel.

RESULTS

In all patients a definite decrease in the white blood cell count occurred during irradiation therapy (fig. 2). The hemoglobin decreased during the latter part of therapy, especially when the chest and mediastinum were irradiated. Both the white blood cell count and the hemoglobin returned to normal after cessation of therapy. Only one patient required a blood transfusion.

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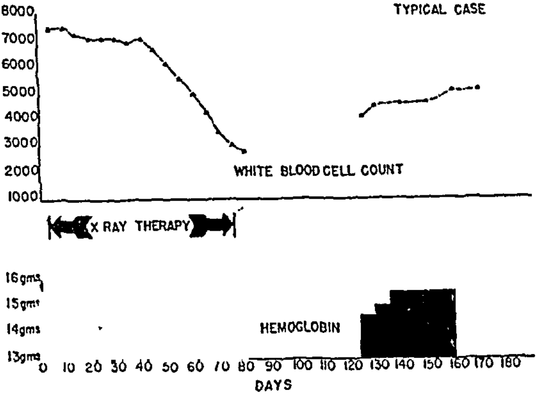

Fig. 2. Typical case showing white blood count and hemoglobin

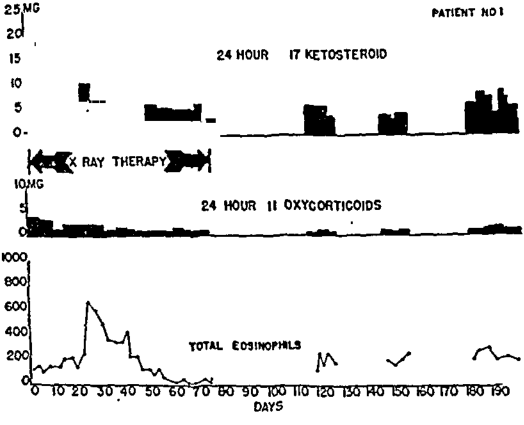

Fig. 3. Group A, typical case

During the first 30 to 40 days of therapy, the eosinophile response to ACTH, in doses of 25 mg. intramuscularly, was obtained. The results were so equivocal that they will not be reported. It was noted that, as the white blood cell count decreased from the effect of the roentgen rays, the eosinophile count decreased also. This made the eosinopenia, which normally occurs after the administration of ACTH (Thorn test) of little value; only the daily eosinophile counts taken at 8 a.m. are, therefore, recorded. In patients in whom a markedly diminished output of urinary steroids occurred, 20 mg. of ACTH administered over a 6 to

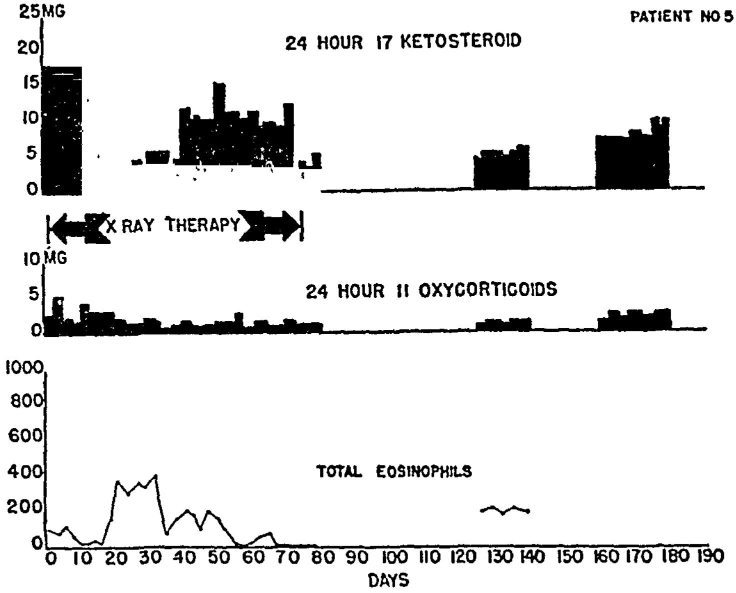

FIG. 4. Group B, typical case

8-hour period did not cause an increase in the 17-ketosteroid output as it did in patients who had only a moderate diminution of the steroids.

The patients can be divided into three groups. Group A (a typical case is shown in figure 3) was comprised of 3 patients. After the initiation of roentgen therapy, there was a constant decrease in the output of the 17-ketosteroids and 11-oxycorticoids. This became most marked when the epigastrium was irradiated. The urinary steroids remained low even after cessation of therapy. There was a slight eosinophilia that lasted up to the fortieth day; the eosinophile count then gradually decreased during the latter period of therapy. Repeated determinations during the convalescent period demonstrated the persistence of this finding. There was a noticeable decrease in the exercise tolerance of this group in comparison with the other groups. The eosinophile counts during the convalescent phase returned to normal as did the white blood cell count. Twenty milligrams of ACTH, given intravenously, did not produce an increase in steroids. Larger doses were not used.

Group B (a typical case is shown in figure 4) was comprised of 5 patients. These patients progressed fairly well throughout the period of roentgen therapy. There was little change in the urinary 17-ketosteroids excretion and only slight elevation of the 11-oxycorticoids during the first 20 days. When the epigastrium was irradiated, there was a marked decrease in the steroid excretion, and this lasted until approximately the fortieth day. During this period, the patients tolerated the roentgen therapy poorly, and a slight eosinophilia was noted. After irradiation of the epigastrium was discontinued, the urinary steroids began to increase and to vary considerably. The eosinophile count and the white blood cell count gradually decreased during the latter period of therapy. The steroids remained depressed upon return of the patients from the convalescent leave but returned to slightly below normal approximately 90 days after cessation of

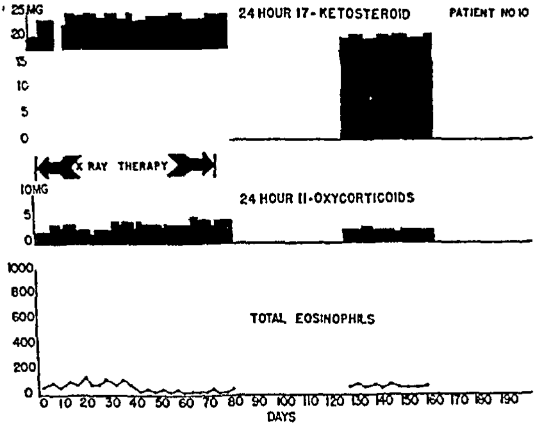

FIG. 5. Group C, typical case

roentgen therapy. Twenty milligrams of ACTH, given intravenously over an 8-hour period, caused an elevation of the urinary 17-ketosteroids before discharge of the patients on the one-hundred-and-ninetieth day. This response to ACTH was small, probably because of the small dosage schedule utilized. All the studies gradually returned to normal by the two-hundredth day.

Group C was comprised of 2 patients (a typical case is presented in figure 5). These patients demonstrated a moderate increase in the output of the urinary 17-ketosteroids beginning after 20 days of radiation and continued to produce increased amounts throughout their course of therapy. There was no diminution in the exercise tolerance. The eosinophile count never became elevated as it did in the two previous groups but remained depressed, especially in the latter phase of roentgen therapy. There was a similar decrease in the white blood cell count during the latter part of therapy, similar to the decrease in the first two groups. The 11-oxycorticoids also were slightly elevated throughout the entire irradiation period. All studies returned to normal within 30 to 40 days after the cessation of therapy. The ACTH-eosinophile responses were not determined in these cases since it was believed that the findings were indicative of a slight hyperfunction of the adrenal cortices.

The symptoms during radiation were weakness, nausea and anorexia, especially when the abdominal area was radiated. These were the most common symptoms and usually occurred after 25 to 30 days of therapy. They were noted mostly in Groups A and B; the patients in Group C demonstrated a minimum of symptoms throughout treatment.

DISCUSSION

The urinary 17-ketosteroids are end products of adrenocortical and gonadal secretions. In the male, approximately two-thirds to three-quarters of the 17-ketosteroids originate in the adrenal cortices, the remainder being supplied by the gonadal tissue. Hyperfunction of the adrenal cortices causes an increase in the output of these steroids; hypofunction causes diminished output in the urine. The 11-oxysteroids are also products of adrenocortical secretion.[9] It is believed that they are derived from steroids that are secreted by the adrenal cortices during stress. The levels of the circulating eosinophiles are intimately related to the activity of the adrenal cortices. Endogenous and exogenous ACTH stimulates the adrenal glands and causes a release of a large spectrum of hormones. An increase in oxysteroids in the blood stream apparently acts directly on the circulating eosinophiles and causes a decrease in their numbers. Roentgen rays destroy white blood cells, and it appears that this effect invalidates the ACTH-eosinophile responses in this study.

The adrenal cortices appear to respond to roentgen rays. In Group A, a marked diminution in the steroid output was demonstrated when the rays were focused over the abdominal area. This change from the normal can be attributed to the direct effect of the roentgen rays on the adrenals, and probably reflects a mild subclinical adrenocortical insufficiency. The failure of the adrenal glands to respond to ACTH confirms this impression. The marked increase in the total circulating eosinophiles during the first 40 days of treatment also represents some impairment of the adrenocortical function, especially in the production of the 11-oxysteroid. In the latter period of therapy, this count becomes invalid because of the direct effects of the rays on the white blood cells in general. In Group B, a depression of the 17-ketosteroids was also evident when the rays were focused over the abdominal areas, especially over the epigastrium. This appears to be the result of the rays on the adrenal cortices.

In Group C, there was a constant increase in the output of the steroids in the urine, indicating a hyperfunction or possible stimulation of the cortices by the rays. The eosinophiles remained normal or depressed throughout. The response in these patients was one of slight hyperfunction of the adrenal glands.

A decrease in urinary steroids is commonly interpreted as evidence of adrenocortical insufficiency. By this standard, the patients in Group A and B had some degree of adrenocortical insufficiency. A patient who has hypofunctioning adrenal glands is a poor risk for any additional stress, such as surgical treatment. If such treatment were indicated, these patients would require supportive adrenal therapy. This is well to keep in mind, not only in patients of the type reported here, but also in patients receiving irradiation over the abdominal area in the treatment of other diseases.

SUMMARY

Ten patients who received large doses of irradiation for malignant diseases of the testes were studied. The urinary 17-ketosteroids, 11-oxycorticoids, total eosinophile count, white blood count, and hemoglobin were analyzed throughout the patient's hospitalization. In all of the patients, a depression of the white blood cell count and hemoglobin developed. This was attributed to the effect of the radiation on the hematopoietic system. A parallel decrease in the total circulating eosinophile count was also seen. There was a direct effect of the roentgen rays on the adrenal glands which caused a diminution in function in 8 of the 10 patients. The remaining 2 patients showed signs of adrenal stimulation. Patients who have had irradiation therapy, especially over the abdominal area near the adrenal glands, should be evaluated for possible adrenocortical insufficiency.

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We are indebted to Capt. Eric Reiss, Miss Margaret G. Haddaway of the Surgical Research Unit, Col. John Richmond, M.C., the entire personnel of the Fourth Army Area Laboratory, also to Mrs. Florence Hocking of Letterman Army Hospital for help in the preparation of this manuscript.

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TESTICULAR METASTASIS FROM CARCINOMA OF THE COLON

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Metastatic tumors of the testicle are very rare. A survey of the literature in 1944 by Helfert and Pinck[1] disclosed less than 50 cases, and they in addition reported one case of testicular metastasis from carcinoma of the prostate. In 1949 London and Grossman[2] reported a case of metastatic carcinoma from the stomach to the testicle, and in 1946 Bandler and Roen[3] described a case of hypernephroma of the kidney with early metastasis to the testicle. In 1941 Kitamura and Horiguti[4] reported a case of metastatic adenocarcinoma to the testicle and skin, but the primary tumor was not found. A survey of the literature for the past 10 years (1943 to 1942) has not revealed any additional cases. A case of metastatic carcinoma to the testicle from a primary in the colon recently occurred in our hospital and is being reported because of its rarity.

CASE REPORT

A. R., a 25 year old Indian man, was admitted to our hospital on July 14, 1952, in a terminal state due to widespread metastases from a primary carcinoma of the transverse colon. In January 1952 he had been operated on at another hospital, the operation consisting of resection of the ascending and transverse colon, part of the stomach and pancreas, and splenectomy. Following surgery, he had a progressively downhill course, with bouts of abdominal pain and vomiting. Three months before admission, he began to have pain in the right costovertebral area and in the spine.

Physical examination on admission revealed a chronically ill male, with marked evidence of weight loss and pallor. There was bilateral cervical lymphadenopathy more noticeable on the left than the right. There was respiratory lag, decreased fremitus, decreased breath sounds, and percussion dullness in the lower third of the left lung posteriorly. The upper half of the abdomen was tense, with a well healed transverse scar extending across the entire abdomen. A hard, round, fixed nodule about 3 by 5 cm. was palpable in the right upper quadrant. The liver was thought to be enlarged, but the edge could not be definitely palpated. There were enlarged lymph nodes in the left supraclavicular and both inguinal regions, in addition to the cervical adenopathy previously mentioned.

Accepted for publication January 21, 1954.

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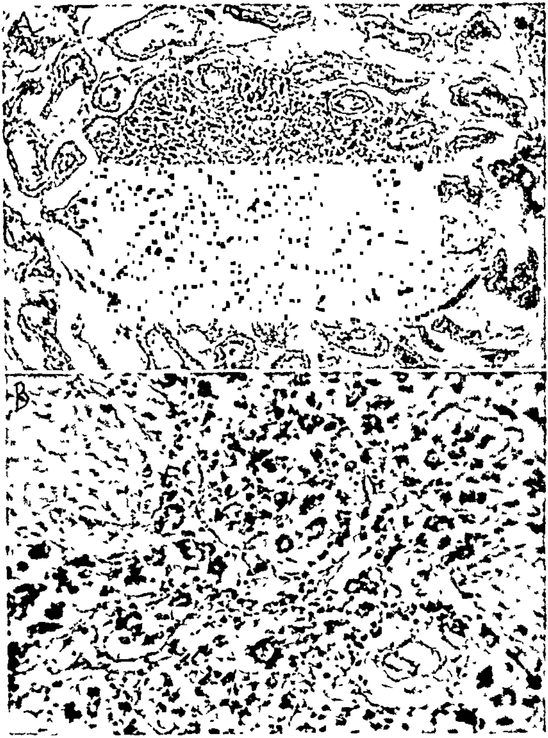

Fig. 1. *A*, low power; showing metastatic nodule surrounded by atrophied seminiferous tubules. *B*, high power; showing acinar nature of metastatic lesion tending to form small atypical glands. Areas in primary had similar appearance.

The entire hospital course was devoted to supportive therapy, including blood transfusions and hypnotics. He expired less than two months after admission, on September 9, 1952. At no time during the patient's stay in this hospital was there any evidence of genito-urinary tract metastases, in spite of the other widespread metastases.

Necropsy examination confirmed the findings of the physical examination. There was marked lymphadenopathy in the areas previously mentioned as well as in the mediastinal and mesenteric lymph nodes. The abdominal cavity contained approximately 2500 cc of amber fluid, and there were many metastatic nodules in the pelvic peritoneum. In the left upper quadrant, the stomach, left kidney, left adrenal, and part of the small intestine were all bound together to form a mass of tumor and adhesions. The liver was much enlarged and full of tumor nodules. The right ureter contained several small tumor nodules, as

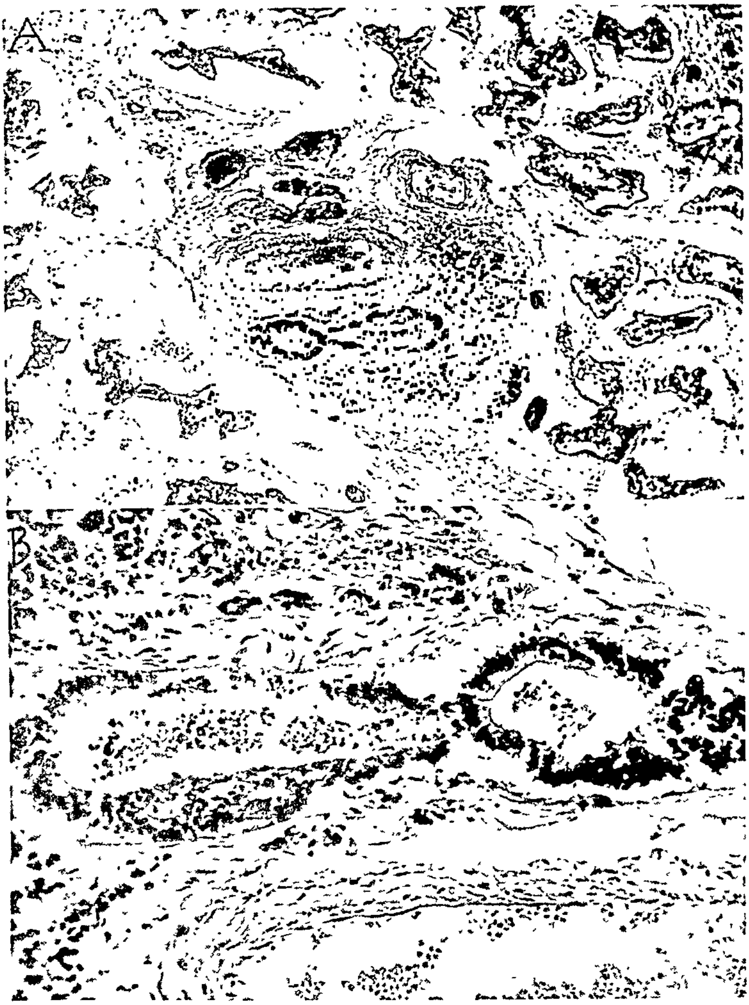

Fig. 2. *A*, low power; showing perivascular, lymphatic spread of tumor. Portions of tumor are better differentiated into type of epithelium seen in colon. Note atrophied seminiferous tubules. *B*, high power; showing tumor lying within lymphatic channel. Epithelium is differentiated into type seen in colon.

did the left kidney. The wall of the aorta showed tumor invasion, apparently limited to the adventitial layer.

In all the sites of metastases mentioned, the characteristic microscopic picture of the neoplasm was seen—columnar epithelial cells with acidophilic cytoplasm and intensely staining dark blue nuclei having an acinar arrangement and with evidence of mucin secretion. In some areas the glandular pattern was not well preserved and some necrosis was seen.

In addition to the aforementioned findings, routine sections through the testicles revealed one small tumor nodule, with the same histological features found in the other sites of metastases (figs. 1 and 2). This area of tumor metastasis was not visible grossly but was very evident on microscopic examination. There was no gross evidence of tumor in either spermatic cord or epididymis, but microscopic sections were not made through these sections.

DISCUSSION

According to Willis,[5] secondary tumors of the testis may occur by one of four routes: 1) by retrograde venous extension or embolism; 2) by retrograde lymphatic extension; 3) by arterial embolism; 4) by direct invasion from neighboring growths.

In the case under discussion, the only one of these four modes of spread which may be ruled out is the last, that of direct invasion, since there were no areas of malignant growth in the vicinity of the involved testicle. Since the left kidney was involved in the tumor mass, it is certainly conceivable that retrograde spread through the left spermatic vein could have occurred. Likewise, because of the tremendous lymph node involvement in the abdomen, retrograde dissemination from the pre-aortic nodes to the testicle might have occurred. It is impossible to state with any degree of certainty, exactly which route of spread of the tumor was important in this particular instance.

SUMMARY

Carcinoma metastasis to the testicle is rare. A necropsied case is reported in which metastasis to the testicle occurred from primary adenocarcinoma of the colon. The possible mode of spread from the bowel to the testis is discussed. Although in this case the metastatic lesion in the testicle was microscopic and not clinically significant, it is conceivable that other metastases to the testicle might occur earlier in the course of the disease, and develop to such an extent that they could well be an important point of clinical, as well as pathological significance.

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CONSERVATIVE TREATMENT OF TUBERCULOUS EPIDIDYMITIS: REPORT OF CASE SUCCESSFULLY TREATED BY LOCAL INJECTION OF DIHYDROSTREPTOMYCIN

PETER J. RIABOFF

Streptomycin, intramuscularly injected, and the newer antituberculosis drugs, have not been found effective in the treatment of tuberculous epididymitis, except as adjuvants of surgery. The present-day treatment of this lesion, therefore, remains surgery: epididymectomy or, if the testicle also is involved, orchiectomy. Since the condition is frequently bilateral, this means emasculation of the patient; hence, any conservative treatment which offers hope of successful results should be of interest to the profession.

In the case to be described, dihydrostreptomycin was injected locally around and into the abscesses and sinuses, with eminently successful results, after intramuscular injections of streptomycin had failed. Although the method has been used in but a single case, the excellent results in that case, and the fact that no similar report could be found in the literature, appear to warrant its presentation.

CASE REPORT

On September 20, 1949, a 52-year-old white man of Spanish extraction consulted the author because of right tuberculous epididymitis. In early childhood he had had tuberculous infection of the cervical lymph nodes, and in 1945 a left nephrectomy was performed for renal tuberculosis and then a ureterectomy, followed by a left orchiectomy.

His present symptoms had commenced 2 weeks before he presented himself, when he noticed swelling of the skin of the scrotum and a lump in the right epididymis. There was no pain or other discomfort.

It was the consensus of the several physicians whom he had consulted that his remaining testicle and epididymis should be removed. One month prior to the present illness, the patient had become engaged and wished to marry as soon as possible. In view of their findings, however, the consulting physicians had advised against this.

The patient was in fairly good physical condition except for the infected right epididymis. The urine was clear. Old scars were present from previous operations on the left side of the abdomen and the left side of the scrotum. The scrotal skin over the right epididymis was edematous, reddened, and adherent to the tail of the epididymis. In the epididymis itself there was a quite firm lump the size of a large grape. Immediately above this was another, smaller lump the size of a bean.

The patient was given daily intramuscular injections of 1 gm. dihydrostreptomycin and 1 tablet daily of chlor-trimeton maleate (4 mg.) orally. In addition, 1 cc (2 units) of crude liver extract was given intramuscularly every 4 or 5 days. (See table 1.)

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TABLE 1

Dihydrostreptomycin, 1 gm. intramuscularly into gluteal region.	Daily from Sept. 20 to Nov. 10, 1949 and on Nov. 18, 23, and 25; Dec. 19; Jan 3, 1950; Feb. 1, 3, 7, 9; May 31; June 2, 7, 1950. (Total, 64 injections.)
Dihydrostreptomycin, ½ to ¾ gm. injected into and around the sinuses and abscesses of the epididymis.	Nov. 11, 14, 16, 21, 28, 1949; Dec. 4, 9, 14, 21, 27, 29; Jan. 3, 11, 16, 1950; May 16, 25, 29; June 2, 5, 9, 1950. (Total, 20 injections.)
Chlor-trimeton maleate, 4 mg., orally.	Daily, Sept. 20 to Nov. 8, 1949.
Crude liver extract, 1 cc (2 units) intramuscularly into gluteal region.	Nov. 30; Dec. 2, 7, 12, 16, 22, 1949; Jan. 5, 7, 9, 13, 18, 20, 23, 25, 27, 1950; May 22, 1950. (Total, 16 injections.)

One month later, the lower abscess broke open, and 9 days later the upper one ruptured. Despite the antibiotic therapy, the patient had two draining sinuses from the epididymis.

As a last resort, it was decided to inject dihydrostreptomycin locally around and into the abscesses and sinuses. From ½ gm. to ¾ gm. of dihydrostreptomycin was thereupon injected at intervals of 3 days to 1 weeks. The injections were given through a fine needle attached to a tuberculin syringe, exercising very light pressure and carefully avoiding injection into the vessels.

The response to this treatment was spectacular. After 5 injections, the sinuses closed entirely, and have remained closed to date. The induration and adhesions gradually disappeared. Encouraged by this progress, the patient was married on November 26, 1949.

On June 9, 1950 (approximately 9 months after the commencement of treatment) all therapy was discontinued and the patient was asked to return for periodical check-ups.

When seen just recently, 3 years after the completion of all treatment, he was in good health and happily married. The epididymis was soft and there were no adhesions to the skin of the scrotum.

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MORE ABOUT INTRAVASCULAR HEMOLYSIS[1]

ROBERT HOUGHTON HEPBURN

The subject of hemolysis, in view of the enthusiasm and exhaustive evidence and reasoning with which it has been approached in the literature is now somewhat of a beaten-up, tired old nag. How could one now use just water! But the fact remains that it is difficult to sell the idea of using nonhemolyzing solutions to "experienced" resectionists who have no trouble (that they know of) from hemolysis. In view of the slightly outraged impatience of respected proponents together with our uncomfortable feeling that we were committing sin, however successfully, and finally to evaluate a genuine doubt whether we were getting hemolysis after all, a group of 36 patients at the Hartford Hospital had immediately preresection and post-resection blood samples analyzed for free hemoglobin (table 1).

Operator 1 had no hemolysis in 7 times at bat. The 15 mg. per cent occurred in preresection samples from several patients and represents hemolysis probably from the small amount of water in the syringe and needle. Operator 2 had 300 mg. per cent and "moderately hemolyzed" in his 2 cases respectively. The quote is the laboratory technician's substitute for a quantitative determination in this case. Since hemolysis becomes grossly visible at about 25 mg. per cent, the term "moderately hemolyzed" is useless from the standpoint of judging the case as having or not having significant hemolysis. Operator 3 was unscathed. Operator 4 used 3 per cent mannitol except in 2 cases and may be considered to have had significant hemolysis in those two. Operator 5 had significant hemolysis in 2 cases. Operator 6 had significant and often marked hemolysis in 6 of nine cases.

Relating hemolysis to grams removed per operator, it is seen that operator 1 had all small resections though no hemolysis. Operator 2, however, had a 10 gm. resection with 300 mg. per cent hemolysis as compared to operator 1's no hemolysis in a 15 gm. resection. This may mean merely that operator 2 was working on a smaller gland to begin with and reached capsule depth after removal of 10 gm., whereas operator 1 may have resected a larger gland and been well away from capsule at 15 gm. Operator 3 had small resections without hemolysis. Operator 4 got hemolysis in small resections with water but, as expected, none in a 32 gm. resection with mannitol. Operator 5 had significant hemolysis in 2 of 3 resections. Operator 6's resections 2, 3, and 6 suggest that with increasing weight of prostate removed, there may be increasing hemolysis. However, his resection 7 shows the greatest hemolysis in the entire series in a resection of but 7.5 gm. This patient had a small, blind, false passage near the prostatic apex to the left of the verumontanum. Did this lead to a venous sinus direct? Parenthetically, in view of what has been said about the danger of low renal reserve being a major reason for use of nonhemolyzing fluid, it is impressive that: 1) This patient's preoperative nonprotein nitrogen stabilized at 85. 2) He had an uneventful convalescence

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[1] Read at meeting of New England Section, American Urological Association, Hartford, Conn. April 30, 1953.

TABLE 1

	1	2	3	4	5	6	7
Hemolysis per operator in milligrams per cent	15 0 0 0 0 0 0	300 M.H.[1]	0 0 0	0 0 0 60 0 75 0 0 0	60 180 0	180 150 585 0 15 825 1020 210 H[2]	0 60 0
Hemolysis in relation to grams removed per operator	15 6 0 15 0 5 0 8.25 0 3.5 0 5.5 0 5.0	300 10 M.H. 36.5	0 7 0 6.25 0 15.5	0 5 0 3.5 0 6.5 60 8.5 0 32 75 3.5 0 7.5 0 5.75 0 11	60 6.5 180 11.0 0 3.0	180 6 150 29 585 32.5 0 13 15 20 825 36 1020 7.5 210 11 H 15	0 8 60 7 0 20
Hemolysis in relation to minutes duration of operation.	15 45 0 75 0 15 0 60 0 40 0 30 0 65	300 35 M.H. 95	0 45 0 50 0 55	0 20 0 20 0 40 60 40 0 110 75 45 0 50 0 55 0 55	60 60 180 60 0 150	180 45 150 60 585 105 0 70 15 90 825 110 1020 45 210 80 H 75	0 45 60 55 0 80

1. M.H. = "moderately hemolyzed"
2. H = "Hemolyzed"

and left the hospital on the fifth postoperative day. 3) He was 80 years old. In other words, here was an oldster with frank chronic renal failure, not just low reserve, who "did fine" with water and hemolysis of 1020 mg. per cent!

Relating hemolysis to duration of operation it is evident that operator 1 need not worry about the time factor within rather broad limits; nor need mannitol operator 4 with his case 6 of almost 2 hours. Operator 2 with hemolysis in a 35 minute case should beware of time. Operator 6 in cases 2, 3 and 6 seems to get more hemolysis with time, but his case 7 made the hemolytic record in only 45 minutes. Evidently operating time may be related to hemolysis but there are more important factors. Incidentally the large figures for time include that consumed by vas interruptions and cystoscopy, not infrequently done, at least in part, by the intern assisted by the attending, and time consumed also by direct visual teaching of student nurses.

The relation of hemolysis to amount of bleeding was not successfully demonstrated since operative notes often omitted reference to bleeding. Quantitative

TABLE 2

	1	2	3	4	5	6	7
Hemolysis in relation to bleeding	15 ? 0 1 0 2 0 2 0 1 0 2 0 2	300 1 M.H. ?	0 ? 0 ? 0 2	0 1 0 1 0 1 60 2 0 3 75 1 0 2 0 1 0 1	60 3 180 ? 0 2	180 2 150 1 585 ? 0 2 15 ? 825 2 1020 ? 210 ? H ?	0 1 60 ? 0 ?
Hemolysis in relation to days to discharge	15 7 0 5 0 7 0 11 0 6 0 D[8] 0 T	300 4 M.H. 8	0 5 0 T 0 9	0 5 0 6 0 5 65 7 0 6 75 4 0 5 0 5 0 7	60 8 180 7 0 R[2]	180 19 150 6 585 5 0 9 15 5 825 12 1020 5 210 5 H 26	0 4 60 7 0 4
Hemolysis in relation to technique	N[3] 28 W[4]	M[5] 28 W	M 28 W	N 28 M[6]	M 28 W	M 28 W	T[7] W

1. T—Transferred
2. R—Repeat cystoscopy for bleeding
3. Nesbit
4. Water
5. McCarthy
6. Mannitol
7. Thompson
8. D—Died

blood loss determinations were not made. The figures recorded are an attempt to reduce such observations as were made to a numerical scale of 5 degrees of increasing severity.

A simple over-all measure of how well patients did should be the number of days postoperative till discharge from the hospital. Hemolysis did not appear related to this figure in these cases. The one patient who died had no hemolysis.*

Case 1 of operator 6 took 19 days because of a clot evacuation and secondary resection. Case 6 of operator 6 had a postoperative sigmoidoscopy by another service. Case 9 of operator 6 was fragile to begin with, had a 12 year history of carcinoma of the prostate, had a wet chest at time of resection, and was delayed in his discharge accordingly.†

Whether the McCarthy type of instrument or the Thompson instrument can be demonstrated to be differently related to hemolysis is a question this small group of cases could not resolve, the Thompson being used in but 3 operations.

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* Autopsy revealed an unexplained adrenal necrosis, old on the left side, fresh on the right. The patient was 65 and had had his left kidney removed for tuberculosis in 1937. Clinically the death appeared uremic though no postoperative nonprotein nitrogen is recorded. The right renal cortex was markedly narrowed; the outer surface was scarred and had multiple retention cysts; the renal vessels were sclerotic.

† He died 8 months postoperative, apparently with inanition; autopsy revealed small kidneys with cortical scarring, a moderate number of obliterated glomeruli, 2 to 3 plus arterial sclerosis, prostatic carcinoma in bone marrow and in one abdominal lymph node.

CONCLUSIONS

Men of 80 plus with diminished renal reserve have withstood hemoglobinemia of 825 and 1020 mg. per cent without symptoms, at least enough to warrant comment in the nurses' notes which in my experience might be called excessively honest if not alarmist.

The operator who used mannitol felt that his patients seemed to have less pep taken out of them by the resection than formerly with water. The visual acuity was negligibly diminished. There was no difference in feel of action of the instrument. Bleeding seemed a little less.

The writer is what might be called a modified capsule hunter and will continue to use mannitol. He believes the bitter-end capsule hunter might advisedly use nonhemolyzing solution, at least when he is getting down to capsule.

The noncapsule hunter is safe with water since he will neither open sinuses nor rupture bladders except possibly in the small glands and contractures. In the latter instance, should there be co-incident shock, such as from a coronary or gastro-intestinal hemorrhage co-incident with the resection, there might well be lower nephron nephrosis with enough damage to result in fatality.

It is not unlikely that use of a nonhemolyzing solution might encourage reversion to more complete resection by those water-men who have become cautious through having had their fingers burned, so to speak, by over-industry. A neater prostatic toilet may be accomplished when unharried by the specter of hemolysis. Finally, the size prostate considered to be the upper limit suitable for resection might well be revised upward, God forbid, by use of nonhemolyzing fluid.

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CLINICAL APPLICATION OF CYTOLOGY TO PROSTATIC CANCER

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Since the development of a technique for detecting cancer cells in scrapings or washings from the various surfaces and organs of the human body, we have interested ourselves in the application of this procedure to the prostate gland. The results of a somewhat critical evaluation of 533 cases which we have studied from the clinical and cytologic aspects are now presented as a preliminary report to a more comprehensive analysis that will be completed at an early date. Our final report will contain a comparative study of the clinical, cytological and serological methods of early detection of cancer of the prostate gland and will further reveal the application of all three for the purpose of early recognition of malignant changes in this gland.

In 1947, when Herbut and Lubin[1] reported on cancer cells in the prostatic secretions, they stated that "according to the Bureau of Census, carcinoma of the prostate is responsible for over 8,000 deaths in the United States every year." Their perusal of the literature disclosed that only in the exceptional clinics are 20 per cent of all cancers of the prostate suitable for radical prostatectomy; that in most clinics this figure is very much lower. In 1950, over 11,339 deaths due to cancer of the prostate were reported.[2]

In 1953, R. H. Flocks,[3] reporting on the treatment of carcinoma of the prostate, stated, "With regard to the fact of the cancer itself, these patients may be divided into three groups: 1) the cancer is limited to the prostate itself; 2) the cancer extends beyond the prostatic capsule into the periprostatic and perivesicular tissues; and 3) definite distant metastases are present. It is generally conceded that from 5 to 10 per cent of the patients with carcinoma of the prostate, as they present themselves to the urologist for care, fall into the first group."

Barnes,[4] in the same year, stated that "a total of 738 cases of carcinoma of the prostate were processed. Fifty-one or 6.9 per cent of these were diagnosed as early. This compares favorably with the 5 per cent to 6 per cent which most authors state is the approximate proportion of prostatic carcinoma which is suitable for radical perineal prostatectomy."

As late as December 1953, John K. Lattimer, et al.[5] wrote: "Carcinoma of the prostate gland ranks a close third among the leading causes of deaths due to cancer in males. Radical prostatectomy for the early localized tumor is the only

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* The Cancer Institute, Miami, Fla.

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[1] Herbut, P. A. and Lubin, E. N.: Cancer cells in prostatic secretions. J. Urol., 57: 542–51, 1947.

[2] Vital Statistics of the U. S., 1950, Part 3, published by U. S. Dept of Health, Education and Welfare, Public Health Service, National Office of Vital Statistics.

[3] Flocks, R. H.: Treatment of carcinoma of the prostate. J. Urol., 70: 491–498, 1953.

[4] Barnes, R. W.: Results of palliative treatment of early carcinoma of the prostate. J. Urol., 70: 489–90, 1953.

[5] Lattimer, J. K., Dean, A. L., Veenema, Ralph and Rafferty, Edward: Radical prostatectomy for cancer. J.A.M.A., 153: 1347–51, 1953.

known method of curing patients with this disease. While all prostatic cancers are curable by surgery for a certain length of time after they first develop, they produce no symptoms during this operable stage. As a result, only a pitifully small proportion of these cancers are discovered and referred to the surgeon early enough to be cured by radical prostatectomy. The great majority (approximately 95 per cent) are inoperable when first discovered, and the patients continue downhill to die in one to five years, despite the palliation provided by orchiectomy, estrogens, or cortisone." They further stated, "Cytological (Papanicolaou and Traut) studies of exfoliated cells in expressed prostatic secretions appear to be of little practical value in patients with small (operable) prostatic cancers, perhaps because the carcinomatous nodules lie in the periphery of the gland."

The foregoing quotations depict a situation as it exists today; increasing deaths due to cancer of the prostate, and no change in the percentage of cancer of the prostate suitable for radical prostatectomy.

We are aware that anatomically the prostate gland does not lend itself to the efficiency of cytology as demonstrated in the uterine cervix. However, because of the present low rate of early detection of prostatic cancer, any method that can increase this rate of detection, regardless of the percentage increase, and a test that can be simply performed, should become a part of a routine physical examination in all males aged 45 and over, regardless of absence of symptoms referable to the genito-urinary tract.

Cancer of the prostate is a disease of the aging, it being estimated that 2 to 5 million men in the United States are afflicted with this condition and without subjective symptoms. The present standards of detection are so inefficient that less than 10 per cent of proven carcinomas of the prostate are in an operable or curable stage at the time of examination. Usually, the symptoms presenting themselves are those of metastases rather than symptoms indicating a lesion confined within the capsule of the prostate.

The efficiency of cytology, as demonstrated by one of us[6] in the detection of early and curable carcinoma of the uterine cervix has led to the hope that this method of detection could be utilized in detecting early cancer of the prostate.

Herbut,[7] in a presentation at the symposia on Exfoliative Cytology, Cancer Detection and Diagnosis at the Medical College of Georgia, in March 1953, stated that "at the present time, cytology of the prostate, instead of being employed as a routine laboratory procedure, is used in selected cases and then chiefly as confirmatory evidence of cancer." Certainly, if this is the situation, detection of early operable cancer of the prostate is relatively impossible, if cytology is to be used only as a confirmatory test of an already existing clinically diagnosed case of cancer, usually inoperable.

However, Willams,[8] in a presentation at the same symposia, was a little more encouraging. He states that "anything added to our armamentarium in diagnosis and interpretation is greatly needed." Yet, in another statement, the role of cytology in the early detection of cancer of the prostate was again relegated to an inferior position as he stated that, "In our armamentarium of diagnosis for carcinoma of the prostate, we first rely upon clinical interpretation of the anatomical changes, that is the rectal palpation of the changes, x-ray for possible bony metastases, chemical for phosphatase levels in serum, biopsies, and now the cytological changes."

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[6] Ayre, J. E [illegible] Stratton, 1951.

[7] Herbut, P [illegible] Cancer Detection and Diagnosis, Me [illegible]

[8] Williams, [illegible] tology, Cancer Detection and Diagnosis, Medical College of Georgia, Augusta, Ga., March 1953.

A review of the literature shows that the multiplicity of cell types from organs other than the prostate gland, presence of infection has made cytology a difficult procedure. Also, the present method of allowing the prostatic fluid to flow onto a glass slide, without previously preparing the slide, had led to many specimens being devoid of cells as they are washed off in the fixing fluid. It has been our practice, in studying this series of cases, to gently tease the prostate gland by digital palpation, being careful to avoid making pressure on the seminal vesicles. The reason for so doing is that a more copious outpouring of prostatic fluid is usually obtained when pressure is not applied to the gland and the contamination of the prostatic fluid by seminal fluid is minimized. It is important that one realize the fact that seminal fluid contamination of these prostatic smears renders cytology studies practically impossible. It is equally important that microscopic examination of the wet prostatic specimen be made in order to determine whether or not infection exists in the prostate gland, for here again pus and bacteria serve as marked inhibitors to adequate cytological examination. Should infection be found, it is better to delay the cytology studies for a short time until appropriate measures have been instituted to eradicate or at least depreciate the severity of the infection. We have handled the problem of preserving as many cells as possible from being washed off by following the well known procedure of putting a thin film of Mayer's albumin over the slide prior to the prostatic fluid flowing onto it. This simple method has increased immensely the number of cells for study.

Another situation that has kept cytology from being more widely accepted is the problem of lack of tissue confirmation. There is a dearth of biopsy confirmation even in clinical cases of cancer of the prostate. In early cancer the problem of biopsy is even greater if the lesion is discrete. Operative procedures are used infrequently and postmortem examinations are not always available.

In our study we have attempted to substantiate our cytologic findings in another way. Recently Cline and co-workers[9] perfected a new method of determining specific prostatic serum acid phosphatase. Their method detects not only metastatic and clinical cancer of the prostate but at least some preclinical cases of cancer of the prostate. Some of these were thought to be confined to the capsule and hence operable. The specific prostatic serum acid phosphatase readings, as developed by Dr. Cline, were performed on a great many patients, plus occasional biopsies, operative material, and occasional postmortem ex-

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[9] Cline, J. K., Director of Cancer Research Department, Medical College of Alabama, School of Medicine, Birmingham, Ala. Personal communications from Dr. Cline as collaborator in a joint study still in investigative stage.

TABLE 1. *Prostatic survey*

Age	No. Cases	Cytology Grading					Unsatisfactory
		I	II	III	IV	V	
30–40	27	17	8	1	0	0	1
40–50	75	34	21	10	0	1	9
50–60	123	36	40	10	4	3	30
60–70	154	42	49	15	7	10	31
70–80	127	28	43	12	12	9	23
80+	27	4	12	1	2	3	5
Total........	533	161	173	49	25	26	99

TABLE 2. *Clinical diagnosis of benign prostatic hypertrophy*

Age	No. Cases	Cytology Grading					Unsatisfactory
		I	II	III	IV	V	
30–40	1	1	0	0	0	0	0
40–50	9	5	2	1	0	0	1
50–60	45	18	15	0	0	0	12
60–70	52	18	22	2	1	2	7
70–80	71	20	27	4	5	0	15
80+	16	3	5	1	1	1	5
Total........	194	65	71	8	7	3	40

aminations which have been used as supportive evidence of our cytological studies.

The usual description of the cell types found in prostatic smears and microphotographs of these cells have been omitted from this paper as they have been admirably and adequately demonstrated by such investigators as Peters[10] and Herbut.[1]

We are presenting our material in a series of statistical tables as follows:

Table 1 shows 533 cases studied up to the present time. A total of 99 cases were unsatisfactory, leaving 434 cases that were cytologically graded. One hundred of these cases were cytologically suspicious or positive. Of these 100, 49 were grade III, 25 were grade IV and 26 were grade V.

We have attempted to correlate the cytological findings to the clinical diagnosis in order to determine if clinical conditions lead to or predispose to early cancer of the prostate (table 2).

In 194 cases the diagnosis was "clinically benign." Of these, there were 8 cases grade III, 7 cases grade IV and 3 cases grade V.

Of our cases 103 had a clinical diagnosis of "prostatitis," and of these 12 were unsatisfactory for inclusion in our report. Of this group 11 cases were grade III, 5 cases grade IV, and 2 cases grade V (table 3).

One hundred sixty-six cases came to us with a diagnosis of "no prostatic dis-

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[10] Peters, Hannah: Usefulness of prostatic smear. J. Urol., 66: 770–7, 1951.

TABLE 3. *Clinical diagnosis of prostatitis*

Age	No. Cases	Cytology Grading					Unsatisfactory
		I	II	III	IV	V	
30–40	6	3	3	0	0	0	0
40–50	21	6	9	4	0	0	2
50–60	31	11	14	1	2	0	3
60–70	30	10	10	3	2	1	4
70–80	13	1	5	3	1	0	3
80+	2	0	1	0	0	1	0
Total........	103	31	42	11	5	2	12

TABLE 4. *Clinical diagnosis was "no prostatic disease"*

Age	No. Cases	Cytology Grading					Unsatisfactory
		I	II	III	IV	V	
30–40	18	11	6	1	0	0	0
40–50	46	24	11	4	0	1	6
50–60	43	15	6	4	2	2	14
60–70	44	12	16	4	2	3	7
70–80	11	2	5	1	1	2	0
80+	4	1	1	0	0	1	1
Total........	166	65	45	14	5	9	28

TABLE 5. *Clinical cancer treated with estrogens*

Age	No. Cases	Cytology Grading					Unsatisfactory
		I	II	III	IV	V	
30–40	0						
40–50	0						
50–60	4	0	3	0	0	0	1
60–70	7	1	1	2	1	0	2
70–80	16	1	7	3	2	2	1
80+	5	1	0	1	2	0	1
Total..........	32	3	11	6	5	2	5

ease," and of these 28 were unsatisfactory. This group showed 14 cases grade III, 5 cases grade IV, and 9 cases grade V (table 4).

Thirty-two of the cases in our study had a diagnosis of clinical cancer and had been under treatment with various estrogens. Five cases were unsatisfactory, while of the remaining 27, 6 cases were grade III, 5 cases grade IV, and 2 cases grade V (table 5).

Thirty-one cases studied by us had a diagnosis of clinical cancer but had received no treatment. Of these, 8 cases were unsatisfactory. This group showed 6 cases grade III, 5 cases grade IV and 10 cases grade V (table 6).

TABLE 6 *Untreated clinical cancer of prostate*

Age	No Cases	Cytology Grading					Unsatisfactory
		I	II	III	IV	V	
30-40	0						
40-50	0						
50-60	3	0	2	0	0	1	0
60-70	*10*	*0*	*0*	3	*0*	5	2
70-80	17	0	0	3	4	4	6
80+	1	0	0	0	1	0	0
Total	31	0	2	6	5	10	8

TABLE 7 *Unsuspected cytologically suspicious and positive cases for cancer of prostate*

Age	No Cases	Cytology Grading		
		III	IV	V
30-40	1	1	0	0
40-50	7	6	0	1
50-60	9	2	4	3
60-70	16	5	4	7
70-80	14	6	6	2
80+	4	0	1	3
Total	51	20	15	16

Of those cases sent to us with a diagnosis of benign prostatic hypertrophy, or prostatitis, or "no pathology," we found 20 cases that showed grade III cytology, 15 cases were grade IV and 6 cases grade V (table 7).

As stated previously, confirmation of suspicious or positive cytology is difficult especially in early or preclinical cancer. While 100 cases were grouped as either suspicious or cytologically positive, 51 of these were in the latter group which are considered to be definitely malignant. Of these 51, 31 had adequate serological studies, and of these 31 cases there were 20 (64.5 per cent) in which the diagnosis was substantiated by elevated specific prostatic serum acid phosphatase determination (Cline method). In 8 cases there was confirmation by tissue examination. Five of these 8 cases were in the preclinical category. These 5 cases had high specific prostatic serum acid phosphatase determinations as well as positive cytology.

DISCUSSION

We have attempted to demonstrate that cytology can be used as an aid in the early diagnosis of cancer of the prostate. Even in suspicious cases, a cytological recheck is easily done and careful watch maintained.

You will note that the incidence of suspicious and positive cytology in benign prostate hypertrophy was 10.7 per cent.

In prostatitis, the incidence was 21.6 per cent.

In "no prostatic disease," the incidence was 19.6 per cent.

It seems reasonable to assume from our survey that benign prostatic hypertrophy is not a precurser of cancer of the prostate, as seen by the low incidence in this series. Furthermore, according to our findings, inflammation does not apparently play a greater role in the cause of prostatic cancer than other factors, as the incidence in normal prostates was found to be about the same as in prostatitis.

In the treated cancer cases, morphological return to normal is not seen in all cases, so that cytology can be used as an index of response to medicinal therapy.

In the untreated clinical cancer, cytology corroborated the clinical impression in all cases that had cells which could be interpreted, and offers a confirmatory method that may eventually be as satisfactory as biopsy.

SUMMARY

The application of cytology to the detection of early cancer of the prostate is re-evaluated.

A method of obtaining cells for study is outlined.

Statistical analysis of 533 cases studied cytologically is given. The source of most of the material used in our study has come from the urologic service of the Jackson Memorial Hospital, while some of the cases came from the offices of private physicians, both urologists and general practitioners.

A detailed report of this study will be in a paper to follow and will embody not only evaluation of the clinical and cytologic determinations for early detection of cancer of the prostate, but specific prostatic serum acid phosphatase determinations.

Papanicolaou grading is used in the tables. Grades I and II are benign, grade III is suspicious, grades IV and V are positive.

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PROSTATIC SARCOMA: SURVIVAL FOLLOWING RADICAL PERINEAL PROSTATECTOMY

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The literature is replete with case reports of prostatic sarcoma but little encouragement has been observed in these reports relative to survival.[1, 2, 3, 4, 5] As has been pointed out by Jewett, radical perineal prostatectomy is a "relatively simple procedure with low mortality and morbidity figures and remains the procedure of choice for early cancer of the prostate."[6] Little has been reported regarding the application of the radical perineal procedure to cases of sarcoma of the prostate. One would anticipate even more favorable reports in the future with extension of radical perineal prostatectomy to include cystectomy and uretero-intestinal anastomosis.

Two cases of prostatic sarcoma subjected to radical perineal prostatectomy following tissue biopsy are reported with a 13 year survival in case 1 and a 4 year survival in case 2. Both patients are living and free of demonstrable sarcomatous lesions.

Case 1. This case was reported by Prince and Vest in 1941.[7] A 52-year-old man who underwent radical perineal prostatectomy on August 27, 1940 for leiomyosarcoma of the prostate is living and apparently free of sarcomatous metastases.

Case 2. A 68 year-old man was first observed at the Johns Hopkins Hospital on February 18, 1949 complaining of increasing prostatism of 2 years' duration. Complete studies revealed the essential pathological process to be an enlarged prostate whose size was estimated at 3 to 4 times normal and in whose left lateral lobe were several areas of localized third degree induration. No fixation of the gland was noted nor was there involvement of the seminal vesicles. A provisional diagnosis of benign prostatic hypertrophy was made with questionable carcinomatous involvement. On February 21, 1949 a perineal biopsy was made of the area of third degree induration. A diagnosis of the frozen section was adenocarcinoma of the prostate. In spite of the size of the gland, a radical perineal prostatectomy was performed removing *en masse* the prostate, seminal vesicles, vasa and bladder neck. The entire specimen weighed 175 gm. On cut section the tissue was white to yellow and consisted of a number of encapsulated nodules, most of which appeared homogeneous in consistency while some were more firm and others soft. The histological appearance of the prostate revealed

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[1] Stirling, W. C. and Ash, J. L.: Sarcoma of the prostate. J. Urol., 41: 515, 1939.

[2] Counseller, V. S. and Bedard, R. L.: Sarcoma of the prostate gland. J. Urol., 43: 836, 1940.

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[5] Riba, L. W. and Wheelock, M. C.: Leiomyosarcoma of prostate. J. Urol., 63: 162, 1950.

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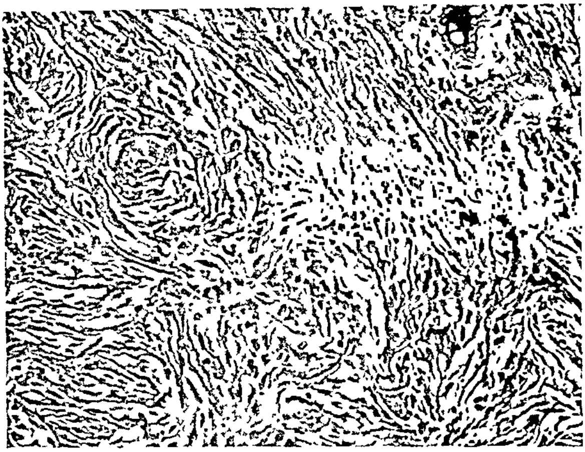

FIG. 1

the presence of strands of cells of malignant character running through the fibromuscular stroma. Many of the glands were hypoplastic. The ducts were dilated and had undergone squamous metaplasia. No invasion of the perineural lymphatics or blood vessels was observed. Examination of sections of the prostate, vas deferens and seminal vesicles revealed only the presence of chronic inflammatory tissue. Sections taken through the firm nodules 2.5 cm. in diameter revealed many spindle shaped malignant cells. These cells were in sheets and sometimes interspersed with the fibromuscular stroma. The diagnosis was sarcoma of the prostate, probably spindle cell (fig. 1).

The patient made a satisfactory recovery with urinary stress incontinence and was discharged from the hospital on March 15, 1949. Three months later he was subjected to perineal exposure and plication of the bulbocavernosus muscles and Buck's fascia in an effort to overcome the incontinence. This was partially successful. Follow-up examination including physical, laboratory and x-ray studies failed to reveal the evidence of recurrence of the prostatic sarcoma.

CONCLUSIONS

Prostatic sarcoma, in spite of its size and location, is amenable to eradication by radical perineal prostatectomy. Two cases of prostatic sarcoma in which the diagnosis had been made preoperatively have survived 13 and 4 years respectively. It is suggested that radical perineal excision of the sarcomatous prostate is the procedure of choice in the management of prostatic sarcoma.

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SARCOMA OF THE PROSTATE: AN UNUSUAL SURVIVAL

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Sarcoma of the prostate is one of the less frequently encountered tumors with which the urologist has to deal. The textbooks describe this subject only briefly and one seldom suspects it instinctively; it therefore is important that every case be reported Approximately 225 cases reported from all parts of the globe have appeared in the literature since the first described by Stafford of London in 1838.

Sarcoma of the prostate is essentially a disease of the first fifty years of life. Thirty per cent of the cases occur in the first decade of life and 80 per cent before the age of onset of benign prostatic hypertrophy. The youngest reported case was four months of age and the oldest 88 years[1] Sarcoma is responsible for one death per thousand due to prostatic malignancy.

There are numerous classifications of prostatic sarcoma with considerable lack of uniformity in the terminology. In fact some persons doubt the existence of true sarcomatous changes in the prostate and choose to classify them as anaplastic, undifferentiated carcinoma[2] A very workable classification proposed by Melicow is one that takes into consideration the tissue origin.[3] Those of fibrous tissue origin seem to be the most common.

The exact etiology of sarcoma of the prostate is not known and, as is true in such instances, there are numerous theories including pre-existing infection, trauma to the perineum, and embryonal maldevelopment. These factors are thought to initiate sarcomatous changes in such intraprostatic foci as fibrous tissue, smooth and striated muscle, and interstitial lymphoid tissue.

Sarcoma of the prostate, when suspected, can usually be diagnosed on the basis of the clinical history and physical findings. Roentgen examination of the long bones for osteoclastic lesions and aspiration biopsy of the prostate may prove very helpful The serum acid and alkaline phosphatase levels are unchanged. The diagnosis is more easily made in the younger age groups because benign prostatic hypertrophy and carcinoma of the prostate are automatically eliminated. Symptoms of progressively increasing vesical neck obstruction culminating in pain and urinary retention are the rule. The tumor often extends posteriorly resulting in obstipation from compression of the rectum. It may also bulgingly present itself perineally or suprapubically Rectal palpation of the tumor gives variable impressions. Frequently it cannot be differentiated from benign adenoma but it rarely is as hard and fixed as carcinoma. It is usually smooth and has been variously described as balloon-like, doughy, or rubbery.

The prognosis is poor. The tumor generally grows and invades rapidly regardless of cell type It is usually outside the capsule by the time it is clinically

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[1] Lowsley, O S and Kimball, F . Sarcoma of the prostate with a review of the literature. Brit J Urol , 6: 328-348, 1934

[2] Boyd, Wm A Textbook of Pathology Philadelphia Lea and Febiger, 1938, 3rd ed , pp 698

[3] Melicow, M M , Pelton, T H and Fish, G W. Sarcoma of the prostate gland Review of literature, table of classification, report of four cases J Urol , 49: 675-707, 1943

manifest. The earliest ones seem to be more malignant and children succumb rapidly. The average duration of illness is nine months.

Treatment includes surgery, roentgen therapy, and combinations of both. There is considerable difference of opinion as to the effectiveness of each.[4, 5, 6] Generally operative procedures are only palliative and frequently roentgen therapy is of no avail. Some authors believe that prostatectomy or any type of surgical trauma will accelerate the rate of growth of the tumor and initiate metastasis.[7] However, it sometimes happens, as in our case, that prostatectomy is of real value, particularly if performed before metastasis occurs.

Mr. A. R., a 61 year old white man, was first seen November 17, 1946 complaining of urinary frequency, hesitancy, slowness, and dribbling during the preceding 12 months. The past history was irrelevant except that in 1941 a physician had told him that he had an enlarged prostate. Rectal examination revealed a grade 4 intrarectal encroachment of the prostate gland thought to be due to benign hypertrophy. For the most part the surface was smooth but scattered nodularities were noted and attributed to adenomatous protrusion. A urinalysis was negative except for scattered white blood cells on microscopic examination. The residual urine was not determined because a catheter could not be passed through the prostatic urethra. One week later, the patient was admitted to the hospital in complete urinary retention and a cystostomy performed. Except for elevation of the urea nitrogen to 30 mg. per cent, the laboratory studies were normal. Subsequently the urea nitrogen returned to normal and a chest x-ray, an electrocardiogram and an excretory urogram were then normal. Two weeks following the cystostomy, a suprapubic enucleation was undertaken. Immediately upon attempting to establish a line of cleavage, it became apparent that we were not dealing with simple benign hypertrophy. The tissue had a firm resilience that yielded no line of separation despite rectal support by the assistant's finger. A collar-like cleavage was finally established about the vesical neck and using this as a starting point, the prostate was finally removed with scissors after two hours of sharp dissection. The postoperative course was lengthy. The patient was finally dismissed on the forty-fourth day with the suprapubic wound healed and control of urination nearly complete. By the end of 3 weeks thereafter complete urinary control had developed and he subsequently returned to gainful employment.

Pathological study revealed the prostate to weigh 270 gm. and to have a rubbery consistency. Microscopic examination revealed myxomatous connective tissue with interspersed fibrous connective tissue and islands of atrophic prostatic gland tissue. Hyperchromatic, multinucleated, giant cells as well as large spindle cells were present (fig. 1, *A*). In co-operation with our pathologist, Dr. M. Oosting, we chose to classify this as a myxofibrosarcoma of the prostate.

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[4] Op. cit., pp. 675–707.

[5] Hess, E.: Sarcoma of the prostate and adjacent retrovesical structures. J. Urol., **40**: 629–640, 1938.

[6] Derian, G. H.: Spindle cell sarcoma of the prostate gland: Case report. J. Urol., **69**: 544–546, 1953.

[7] Melicow, Op. cit., pp. 675–707.

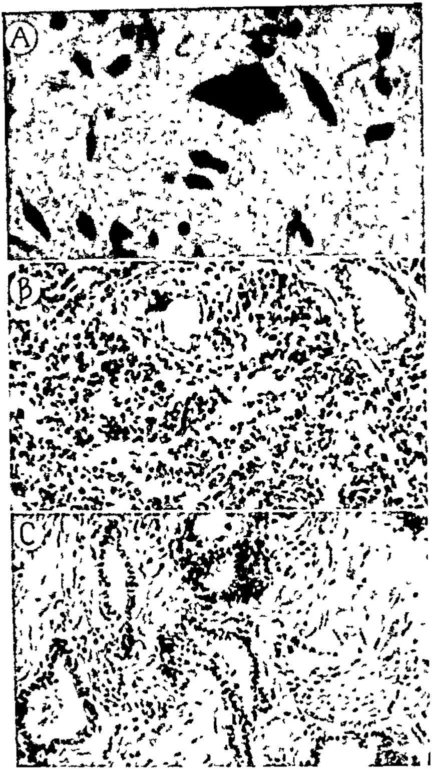

FIG. 1

The patient was seen about twice yearly thereafter usually because of an episode of low grade urinary tract infection. In November 1948 a panendoscopic examination revealed tissue protruding into the prostatic urethra from the left side but not obstructing urinary outflow. The patient was last seen perfectly well on October 22, 1949.

On April 4, 1953 he was admitted to the hospital by an internist with severe respiratory difficulty and a history of progressive personality changes during the preceding two or three weeks. A chest x-ray revealed a space occupying lesion in the right lower lung. The patient subsequently slipped into coma and expired on April 21, 1953, approximately 6½ years following prostatectomy.

Postmortem examination revealed a tumor near the periphery of the right lower lobe of the lung and tumor thrombi in the cerebellum. Microscopic study of the tumor revealed a primary oat-cell carcinoma (fig. 1, *B*). The bladder and prostate were negative except for a nodule in the prostatic fossa measuring 3 cm. in diameter. Microscopic study revealed it to be hypertrophied, nonmalignant prostatic tissue (*fig.* 1, *C*).

In summary, we have re-emphasized the main points in the incidence, classification, etiology, diagnosis, prognosis and treatment of sarcoma of the prostate. We have described a case of myxofibrosarcoma of the prostate treated by prostatectomy alone; the patient died 6½ years later of an unrelated malignancy. We have also noted that the autopsy revealed no evidence of sarcoma in the prostate but did reveal a nodule of benign hypertrophy.

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WATER AND ELECTROLYTES IN UROLOGICAL PATIENTS

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This aims to be a concise, practical discussion of fluid and the principal electrolytes in sick patients, and will be limited to water, sodium, chloride, bicarbonate, potassium, and calcium. The last will be considered only as an elctrolyte.

The average normal adult in ordinary circumstances takes in about 1500 cc of water as such, and derives 1100 from his food, partly preformed and partly the result of oxidation. He requires about 4 gm. each of sodium and potassium chloride, but usually takes 8 to 15 gm. of the first and 6 to 9 of the second. He requires about three quarters of a gram of calcium per day.

In a man of 70 kilograms about 50 per cent of the body weight or 35 liters is intracellular water. About 22 per cent or 14 liters is extracellular water, 11 liters being interstitial, and 3 liters intravascular (the plasma). His body contains 135 gm. of sodium chloride, and 160 gm. of potassium. The calcium of the plasma aggregates only about 0.3 gm.

As clinicians we are concerned mainly with the plasma because its constituents are readily measured; those of the interstitial and intracellular spaces are not. The electrolytes in which we are interested are present normally in the following amounts:

Ion	Milligrams or Volumes Per Cent	MEQ/L.	Conversion Factor
Na	325	142	2.3
Cl (as NaCl)	600	100	6.0
$HCO_3(CO_2)$	56	27	2.2
K	20	5	4.0
Ca	10	5	2.0

Milliequivalents per liter means milligrams per liter times valence divided by atomic weight. This measure is preferred by biochemists because the anions (base) and cations (acid) of the plasma each add up to 155 milliequivalents; thus mEq. per liter express shifts in the various constituents while milligrams per cent do not.

In ordinary circumstances the urine of a normal individual in an average environment will total 1500 cc of water containing 3 to 5 gm. of salt per liter. In addition there is the "insensible loss"—perspiration 600, expired vapor 400, and stools 100 cc. A two degree rise of temperature can double the insensible loss.

Maximal losses under extreme conditions may be enormous. Thus sweat may

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add up to as much as 14000 cc with 35 gm. of salt in a day. Saliva may total 1500 with 8 gm. of NaCl; the gastric juice 2500 with 18; the bile 500 with 4; the pancreatic juice 700 with 6; and the intestinal juices 3000 cc with 22 gm. A patient with nasal suction *and* diarrhea may actually lose 7000 cc of fluid and 50 gm. of salt per day through these channels alone.

The interchange between the intracellular, interstitial, and vascular compartments of fluids and electrolytes depends upon their osmotic pressures, and upon that of the proteins; upon the selective permeability of the cell membranes, and upon the influence of hormones. Their concentration depends upon intake and losses, and upon renal excretion, which is regulated by the need to maintain the isotonicity and neutrality of the fluids of the body. The kidneys accomplish this through selective secretion and re-absorption of the glomerular filtrate by the tubular epithelium, and by the formation in the tubules of ammonia for the neutralization of acids. The exhalation of carbon dioxide is also important in the excretion of excess acid.

The concentrating ability of the kidneys is of great importance: a kidney which can concentrate to 1.032 can get rid of 35 gm. of waste in 500 cc of water, while one which can concentrate only to 1.014 will require 1500 cc. Thus a urine output of 1500 cc per day is important as a factor of safety in a sick patient.

The neutrality of the blood before excretion is maintained by the buffer system. Thus the bicarbonate of the plasma can combine with acids to form neutral salts and carbonic acid, which is given off in the lungs. It can also combine with alkali to form sodium carbonate and water. The phosphates exert a similar but weaker effect by shifting between the disodium (alkaline) and monosodium (acid) forms. Hemoglobin becomes more acid as it takes up oxygen in the lungs, driving off carbon dioxide; as it loses oxygen in the tissues it becomes less acid and is able to take up carbon dioxide. The proteins participate in the regulation of the pH of the blood because their amino groups can combine with acids and their carboxyl groups with alkalis.

Disturbances in the equilibrium of water and electrolytes can be anticipated in patients with impaired renal or cardiac function, and in those with protracted anorexia, vomiting, nasal suction, diarrhea, and excessive sweating (fever and toxemia).

Alkalosis is rare in urologic patients. It results from loss of acid, as in hyperventilation of psychogenic origin; from persistent loss of the gastric juice (prolonged nasal suction or vomiting); or from the excessive ingestion of alkali. It is characterized by hyperpnea, muscular twitchings, and increased muscular irritability like that of hypocalcemia. The carbon dioxide combining power of the blood is increased.

Acidosis is far commoner. It may result from loss of base during diarrhea; from inability to neutralize acid, or from excessive ingestion of it in the presence of renal disease which prevents the formation of ammonia intended to neutralize the acid. Hyperchloremic acidosis occurs in certain diseases of the renal tubules, and particularly after ureterosigmoidostomy.

Acidosis is characterized by hyperpnea intended to increase the elimination of CO_2, and often by the manifestations of concomitant uremia and dehydration. The CO_2 combining power of the plasma falls.

Depletion of water without loss of electrolytes is very rare and may be ignored for our purpose.

Depletion of NaCl and water is invariably associated with dehydration except in patients who have lost both but have then received water orally or solutions of glucose intravenously. It is especially likely to occur in vomiting, excessive sweating, diarrhea, severe postoliguric diuresis, and in adrenal insufficiency.

When salt is lost, water is excreted to maintain isotonicity; if water is then administered, the blood again becomes hypotonic, and more water is excreted, aggravating the situation. The volume of the blood is reduced and its viscosity is increased. Circulatory collapse may then result. In addition there may be atony of the stomach and spasm of the pylorus; if so, more fluid and electrolytes pour into the stomach (acute gastric dilatation) and the situation is worsened. The combination is likely to be fatal especially if gastric dilatation is not recognized.

Such a patient first exhibits lassitude, headaches, and dizziness with anorexia. He is *not thirsty*. After the loss of fluid exceeds five per cent of the body weight, the skin becomes wrinkled and the eyeballs soft and shrunken. Cramps and delusions precede collapse. Chloride disappears from the urine*, and the sodium and chloride of the plasma fall. The possibility of gastric dilatation should always be investigated by aspirating the stomach.

Retention of salt and water results from impaired renal function or cardiac decompensation with oliguria. It is also seen with the hypoproteinemia of starvation, of severe and extensive burns, and of profound toxemia. Here salt is retained to replace the osmotic effect of lost protein. It may be induced or aggravated by the administration of the salt-retaining hormones in descending order: DOCA, cortisone, ACTH, estrogens, and androgens. The oral or intravenous administration of NaCl will, of course, greatly aggravate the effects of any of these situations.

The condition becomes evident clinically when the gain of body weight exceeds 10 per cent. The bedridden patient first exhibits edema of the scrotal and sacral areas; the ambulatory one shows it first in his ankles. Both later may have râles and dyspnea.

TREATMENT

The objectives of treatment are to restore the proper balance of water and electrolytes, and to achieve and maintain a daily urinary output of 1500 cc containing at least 3 gm. of salt per liter. The following techniques are useful:

1) Frequent observations of the patient with emphasis upon the turgor of the skin and of the respiratory rate.

2) Accurate measurement of the daily volume of urine.

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* Place ten drops of urine in a clean test tube and add one drop of 20 per cent potassium chromate. Add 2.9 per cent silver nitrate one drop at a time with thorough shaking. A change from yellow to brown is the end point. If it appears with the first drop, chlorides are absent. Each drop required to produce the end point represents roughly one gram of NaCl per liter of urine. Less than three grams per liter suggests depletion of NaCl (Fantus).

3) Daily weighing of the sick patient. When not eating he should lose weight very slowly. A sudden gain of more than 2 per cent suggests retention of salt and water (7 gm. of NaCl will hold a liter of water). A sudden reduction suggests dehydration with a concomitant loss of salt. Remember that a two degree rise of fever doubles insensible loss of fluid.

4) Measurement of urinary chlorides when depletion is suspected. It is cheap and quick.

5) Determination of the renal function, plasma chlorides, and CO_2 combining power in sick patients.

PROPHYLAXIS IN POSTOPERATIVE PATIENTS

As an example let us take a patient who has had a protracted, rather bloody nephrectomy for neoplasm. The loss of blood during operation has been determined by weighing the used sponges, and has been replaced. Since some gastrointestinal distention has been observed toward the end of operation, nasal suction has been instituted. Shock is absent.

One thousand five hundred cubic centimeters of 5 per cent glucose and 500 cc of normal saline (4 gm. NaCl) are started intravenously immediately after operation to replace the insensible loss of fluid plus that evaporated from the wound during operation. The salt represents that not taken in the food; it is less than the normal requirement because salt is likely to be retained for a brief period after operation.

Next day the temperature is normal. The urine totals 1000 (3 to 5 gm. of NaCl); 500 cc have been removed by nasal suction (about 3.5 gm. of salt); 1000 cc of water have been lost through lungs and skin, and none through the stool. The patient should therefore receive 2500 cc of fluid and 6 to 8 gm. of salt.

Requirements of succeeding days are calculated and met in a similar fashion until the patient is eating and drinking normally and excreting a normal amount of urine.

Complications such as fever, excessive sweating, diarrhea, and oliguria are dealt with according to data supplied in previous pages, a sudden gain in weight calling for reduced fluid and salt intake until the cause has been found and corrected, while a sudden loss suggests dehydration and appropriate measures to correct it. If nasal suction is used for more than two days, potassium chloride (see below) is added to the intravenous fluid; it is probably wise also to add thereto about twice the minimum daily requirement of B complex and vitamin C each day. Wounds which exude a great deal of fluid (as after cystectomy) call for measurement of the plasma protein lest a large loss escape attention. A significant loss of water may occasionally occur by this route.

SPECIFIC IMBALANCES

Depletion of salt and water. Wrinkled skin with poor turgor; rapid loss of weight; urinary chlorides low or absent; plasma sodium and chlorides reduced; renal function usually good. The blood pressure may fall. Give 1000 cc of normal saline during the first hour; 500 during both the second and third hours; and

300 cc per hour for 3 hours more. If dehydration is slight, use 2 to 3 per cent saline. In either case, stop when the urinary chlorides reach 3 gm. per liter. If dehydration is severe, switch to half normal saline and 2.5 per cent glucose as soon as chloride appears in urine, and continue until they are normal. Do not continue to administer salt if there is a rapid gain in weight without a rise in urine output, but measure the plasma protein and chlorides, and renal function.

Remember that in hypochloremia, the administration of 0.5 gm. of NaCl per pound of body weight will raise the plasma chlorides by 100 milligrams per cent of 17 mEq. per liter. If in doubt, stop the salt.

Retention of salt and water. One finds edema, dyspnea, a low urine output, and often impaired renal function. Therapy aims at improved renal and cardiac function. Diuretics may be used if renal function is good, but watch out for hypochloremia if a large diuresis occurs. Measure the plasma protein if no diuresis develops. With moderate diuresis one may give water freely by mouth or ten per cent glucose intravenously.

Acidosis. This is best recognized by measuring the plasma bicarbonate in patients who have diarrhea, oliguria, or other evidence of damaged kidneys. Diarrhea should be stopped; renal failure should be treated if possible; acid intake should be reduced; and continuous irrigations of the colon should be employed in the presence of ureterosigmoidostomy. The acidosis of prostatism with moderately impaired renal function will correct itself if free drainage and forced fluid are supplied. In severe acidosis, Kagan's formula may be used with advantage: 55 minus CO_2 combining power in volumes per cent times the body weight in pounds (or 30 minus CO_2 in mEq. per liter) equals cubic centimeters of 1/6 molar sodium lactate intravenously. This is used when dehydration is prominent. When it is not, one fourth of the above volume of 5 per cent sodium bicarbonate may be used instead. Do not repeat either of these without another measuement of the CO_2 combining power. The danger of overloading with sodium when urine output is poor must be remembered.

Alkalosis is usually characterized by vomiting and hyperpnea. One should measure the plasma chlorides and replace the deficit according to Kagan's formula. In severe cases (CO_2 combining power of 90 to 120 volumes per cent or 40 to 55 mEq. per liter) give 0.1 cc of 5 per cent calcium or ammonium chloride per pound of body weight intravenously. In mild cases an ampoule of calcium gluconate intravenously may suffice. Be guided by the CO_2 combining power.

In summary, rely upon: the clinical state of the patient, the daily weight, the output of urine and of urinary chlorides, and upon the chlorides and CO_2 combining power of the plasma. Use oral fluids where feasible.

POTASSIUM

The body contains about 160 gm. of potassium, most of it being in the cells with only 2.7 gm. in the plasma. The normal level is 20 milligrams per cent or 5 mEq. per liter. It is important as a base, but is vital in that, in equilibrium with calcium and magnesium, it determines the irritability of striated muscle. This is of especial importance in relation to the cardiac muscle, where either an excess or a lack may cause cardiac arrest. Since the normal kidney excretes potassium at a constant minimum rate even in the absence of intake, starvation will ultimately induce hypokalemia. The gastric juice contains up to 40 and the intestinal juices up to 10 mEq per liter. Therefore, prolonged vomiting, nasal suction, and diarrhea will produce hypokalemia quite rapidly. It should be anticipated in such circumstances, especially in young and in diabetic patients.

The patient with hypokalemia complains of anorexia and weakness, especially of the lower extremities, which may become flaccid. The electrocardiogram shows changes readily recognizable by the cardiologist when the serum potassium falls below 2 mEq per liter. It can be corrected by the oral administration of orange or tomato juice or of Valentine's meat juice. Six to 9 grams of potassium chloride per day can be added to the first two, or it can be mixed with the intravenous fluid (2 to 5 gm. per liter). Its rate of intravenous administration should not exceed 180 drops per minute lest temporary hyperkalemia cause cardiac arrest. Since administered potassium reaches equilibrium in the cells very slowly, and since a small deficit in the serum may represent a large one in the cells, treatment must be vigorous, and continued until electrocardiogram and serum potassium are normal. The intake must then be maintained. The intravenous administration of saline to a patient with hypokalemia may be rapidly fatal because it drives potassium out of the circulation and into the cells. The use of adrenal cortical hormones has a similar effect, since they cause retention of sodium and excretion of potassium.

Hyperkalemia accompanies severe tissue damage as in extensive trauma to muscle and in severe hemolytic reactions; it is seen in oliguria and chronic uremia, and in Addison's disease. Clinical manifestations include paresthesias, muscular weakness and twitchings and, curiously, flaccid paraplegia. The electrocardiogram shows typical changes, and the serum potassium rises. Ten mEq/liter is a dangerous level.

Primary aim of treatment is improvement of renal function. While this is being attempted, one may give calcium gluconate intravenously for its specific antagonism to potassium; if urine is being excreted, 10 per cent glucose with 30 units of insulin per liter may be given intravenously to drive potassium out of the circulation and into the cells. If the kidneys fail to function, dialysis should be used in reversible renal lesions. In adrenal insufficiency, NaCl, desoxycorticosterone, and cortisone are required.

CALCIUM

We are not concerned here with hyperparathyroidism nor hypercalcinuria, nor with the clotting mechanism, but only with those uncommon situations in which calcium is lost as a fixed base. The normal need for calcium is about 0.75 gm. per day. Its absorption from the bowel is facilitated by the presence of vitamin D, acids, citrate, and bile, and impaired by the presence of alkalis and of an excess of phosphates. Excretion stops when the level in the serum falls below 7 mg. per cent. There is an abundant reserve in the bones.

While it is excreted in excess in atrophy of bone, idiopathic hypercalcinuria, and hyperparathyroidism, these disorders do not lower the level in the plasma. We are concerned mainly with protracted hyperchloremic acidosis, which has so depleted the stores of sodium that calcium is used as a base for the excretion of acids, and with uremia, in which retained phosphates combine with calcium to form an insoluble compound.

Symptoms include fatigue, hyperirritability, muscular twitchings, carpopedal spasm, and a positive Chvostek's sign. The serum calcium is low.

It is treated where possible by the oral administration of milk and vitamin D. Where this is not feasible, one may give calcium gluconate intravenously and dihydrotachysterol 1 to 3 cc orally per day (1.25 to 3.75 mg.).

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SOME PSYCHIATRIC ASPECTS OF SYMPTOMS OF GENITO-URINARY DISEASE

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The purpose of this presentation is to describe symptoms common both to psychiatric and urological disorders and to suggest how the urologist, who frequently is consulted first, can improve the psychiatric state of suitable patients.

Psychiatric disorders are broadly separated into two main categories, the psychoses and the psychoneuroses (synonymous with neuroses). The psychoses are characterized by a serious failure to appreciate reality. They comprise those psychiatric illnesses which constitute legal insanity and incompetence either during some phase of the illness or throughout its entire course. During such an illness the patient may have hallucinations or delusions, be in a violent panic or suicidal. We do not deal with these conditions in this study.

The psychoneuroses, which presently concern us, are psychiatric disorders in which the personality is dominated by anxiety, obsessional thoughts, compulsive acts, fears and physical complaints in various patterns without objective evidence of organic disease.

Anxiety neuroses are manifested by feelings of restlessness, tenseness and anxiousness accompanied by palpitation, sweating and cold extremities.

Obsessional thoughts are ideas that repeatedly recur to the patient despite his manifest desire to dismiss them.

Compulsive acts are actions performed by a patient against his will as the result of an inner necessity. When these constitute the chief complaint, the syndrome is called an obsessive compulsive neurosis.

When fears dominate the personality, such as fear of crowds, fear of closed spaces, fear of animals or inanimate objects, the condition is termed phobic reaction.

If physical complaints without objective evidence of disease are the main complaints and dominate the patient's personality, the syndrome is usually called hypochondriasis.

If there are conversion symptoms such as glove anesthesia of the hand, midline anesthesia of the chin or hysterical paralyses, the syndrome is called conversion reaction. Instead of being experienced consciously, the anxiety impulse is "converted" into symptoms of dysfunction in organs or parts of the body which are usually under voluntary control. These symptoms lessen conscious anxiety and usually are symbolic of the underlying mental conflict. Such reactions usually meet immediate needs of the patient such as the guilty need to be babied met by a conversion hemiplegia.

Schizoid is another common diagnostic expression. It designates an exceed-

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ingly shy, seclusive, more or less retiring individual who is excessively withdrawn and introverted. He may or may not suffer from any of the other neurotic complaints.

A number of symptoms commonly produced by organic diseases of the genito-urinary organs may also accompany neuroses. Among these symptoms are pain (often in the penis and localized near the glans or along the course of the urethra), frequency, urgency, retention of urine, polyuria, oliguria, nocturia, enuresis, "chronic congestion of the prostate" sometimes with an ache in the testes, impotence and sterility. In addition, there may be anxiety concerning the condition of certain organs such as the size of the penis or testes. Of these symptoms, those with the most frequent and important psychiatric aspects are enuresis, impotence and urinary frequency.

Every experienced urologist knows that it is not uncommon for patients with some degree of mental unbalance to present one or more of these symptoms, and that in such cases accurate diagnosis and successful treatment are especially difficult. It is likely that few of these patients now receive satisfactory treatment because most urologists are too busy or too impatient to listen to their apparently unreasonable recitals and most psychiatrists are unable to give adequate help. This paper, therefore, will briefly discuss differential diagnostic procedures and describe simple psychotherapeutic measures practicable for the urologist to apply.

We believe that the psychiatric difficulties of a large proportion of these patients are amenable to simple treatment when they first seek medical advice. Since the urologist usually has the first opportunity, he should accept the responsibility for affording relief whenever possible unless the psychiatric derangement is beyond his ability to treat, when he should promptly refer the patient to a competent psychiatrist.

Regardless of his attitude toward treating simple psychiatric problems associated with symptoms of genito-urinary diseases, the urologist must carefully avoid producing further psychiatric illness in his patients. Forcefully advocated and frequently repeated treatments, such as dilatation of the ejaculatory ducts, dilatation of the ureters, or even overdoing prostatic massages, may strengthen neurotic illnesses or produce them, especially in predisposed individuals.

The only way by which the urological or psychiatric significance of symptoms common to both fields can be truly recognized is by means of a careful history and physical examination. One should never use the "either-or" basis to differentiate psychiatric manifestations from organic disease of the genito-urinary system because the possible association of significant psychiatric imbalance is not necessarily excluded when organic disease has been found and vice versa. For instance, pain often is a symptom of great urological significance; it may also be part of a psychiatric syndrome. A psychiatrist may note the conjunction of burning in the penis with hysterical symptoms and make the diagnosis of hysterical pain. While this diagnosis could be correct, the possible presence of acute urethritis or prostatitis cannot be ruled out without further investigation.

Pain in the penis, described as a "burning sensation" which may be caused by prostatitis or urethritis, also is occasionally the chief complaint of individuals suffering certain kinds of anxiety and tension. Patients with syphilophobia and cancerophobia are examples of this group. Their complaints usually fit into the syndrome called phobic reaction, described above. All of the complaints of these individuals are likely to be exaggerated and dramatic. Some of these men and women go from one physician to another, apparently convinced that they are suffering from a terrible disease and they remain adamant in that conviction in spite of medical evidence to the contrary.

Frequency and urgency which may be caused by a urinary tract infection, prostatic enlargement, a stone or a tumor in the bladder, are also commonly associated with, and the result of, simple acute anxiety reactions. These are such as occur preceding a serious examination in medical school, or before entering military combat or some other threatening situation. Frequency and urgency may also be manifestations of some chronic anxiety or tension states such as may occur in a variety of psychiatric syndromes, especially in the schizoid individual with hypochondriasis. This type of patient is extremely shy, withdrawn, suspicious and complains bitterly of his symptoms and how everyone has completely failed to help him. He may even suggest that he has been injured or made worse by his previous physicians. The prognosis is poor for improvement with any kind of treatment although it is possible to maintain the economic and social status of these individuals by patient palliative treatment over many years. These patients often consider themselves insulted and will seek treatment elsewhere if psychiatric therapy is urged. However, they are likely to be more amenable if they have specific psychiatric complaints such as insomnia, depression, fears or severe anxiety.

Retention of urine, usually caused by organic obstruction of the bladder outlet, occurs occasionally on an entirely psychogenic basis due to a spasm of the sphincter muscles. This is analagous to that which occurs in the rectum, the sphincter of Oddi, and the cardiac sphincter of the stomach. The precipitating emotional stress may be obscure and impossible to find in a short history, but the condition is usually recurrent. A woman who declared that she could not void was cured when a retention catheter was left in the bladder for 72 hours. The urologist in charge who knew the healthy condition of her genito-urinary system, gave the patient no additional treatment other than listening with patience to her complaints.

Difficulty in urination may consist of hesitancy in starting the stream, difficulty in maintaining a constant flow or sudden stopping of the stream. These symptoms may be the result of prostatic enlargement, urethral stricture, bladder stone or tumor, or they may occur when some organically normal individuals attempt to urinate in the presence of others. This trouble was not uncommon among extremely shy individuals in the armed forces and a number developed neuroses from their anxiety in the common toilet. It was a more serious illness if, at the same time, there was similarly induced bowel dysfunction. Difficult urination may also be a reflex nervous disorder in individuals who are under extreme tension of the type characterized by "have to get it over with." They are so impatient and angry with any delay in completing the task at hand that they can barely relax enough to start and maintain their stream. They may stand and strain with a great sense of annoyance until finally they are relieved.

Polyuria may be temporary due to excessive fluid intake, cold, suppression of sweat, the use of diuretics, the crisis of a fever, hysteria or nervous excitement. Polyuria often is permanent in diabetes mellitus, diabetes insipidus, chronic interstitial nephritis, and in amyloid disease of the kidneys. There is a psychogenic type of polyuria produced by an excessive water intake due to an exaggerated thirst. The occasional individuals so affected find their only relief from severe anxiety in the frequent and abundant intake of water and other liquids.

Oliguria may occur with cardiac or renal failure and also in association with dehydration experienced by patients in catatonic stupor, prolonged severe excitement states and anorexia nervosa. It is important to make a correct diagnosis promptly because these patients are seriously ill and the proper treatment for the different conditions varies greatly. Diagnosis may be difficult if the patients are unconscious but examinations of the blood usually will show retention of nitrogenous waste products, characteristic of uremia. Since kidney failure can be due to so many conditions such as obstruction of various types, stone, tumor, nephritis, circulatory failure, or the ingestion of poisons, much further investigation must follow the establishment of an organic basis for the oliguria. On the other hand, as soon as the heart and kidneys are found normal, the dehydration can be overcome with proper quantities of fluids administered intravenously.

Nocturia, when of organic origin, commonly appears in men of middle age in the earlier stages of prostatic obstruction. It occurs frequently in children who rationalize their nightly visits to their parents' bedroom by saying that they had to go to the toilet. It may also occur as an expression of marital anxiety in which one partner escapes from uncomfortable, physical intimacy by a trip to the toilet.

Chronic prostatitis or "chronic congestion" as it is sometimes called, may be a manifestation of inflammation due to infection or symptomatic of unfulfilled erotic excitement. It has sometimes been referred to as the sudden abstinence syndrome occurring when the wife is pregnant, ill, or away from home. A quite different type occurs in the homo-erotic patients who become addicted to prostatic massage to relieve their erotic tension.

Enuresis, and unless controlled, can wreck the life of its unfortunate victim, has been recognized for many years as being of exclusively psychiatric nature in 75 to 95 per cent of the cases. However, with the development and use of suitable instruments for visualizing the posterior urethra in young children, an increasing proportion of patients have been found with demonstrable organic abnormalities and have been cured by endoscopic treatments. In so far as enuresis is a manifestation of an emotional disturbance in the child, one can presume that it reflects some kind of tension in the relationships between the mother, father and child. It is useful to make a tentative exploration of these relationships before referring the child for a psychiatric evaluation. In each instance the psychiatric study should include the parents. Perhaps explaining the disturbing factors to them may end the stress on their child with improvement in the enuresis.

Impotence has also had an abundant literature. To the extent that it is an exclusively psychiatric problem, it is an expression of a disturbance in the area of the physical intimacy. A minutely detailed history of where, when, how and what is particularly important here. Impotence is always present in a serious depression. It may also be a part of almost any other psychiatric syndrome. It occurs at times in individuals who suffer from hysteria, chronic anxiety, hypochondriasis, obsessive compulsive neurosis, phobic reactions and psychotic reactions.

Sterility has at times been blamed on "nervous exhaustion" when no other cause could be specified. These "idiopathic" cases sometimes become fertile after adopting one child. This strongly implies some kind of an emotional problem as an etiologic agent. Perhaps this will be understood better as the interrelationships of the sex hormones with the adrenal cortical hormones and stress become better clarified.

Patients, particularly parents, may complain of "excessive" masturbation. If parents, they complain about their children usually. Masturbation is entirely normal. If practiced so conspicuously that the parents notice it and bring the child to a doctor, the child must be suffering a serious emotional problem or complete lack of privacy. If the adult complains about doing it himself, the important question to ask is why is he complaining. Is it because he is so lonely? These individuals are usually quiet, shy and withdrawn. They are often more or less ashamed of their "wet dreams". Occasionally an individual has been alarmed because of a seminal discharge occurring while asleep which was mistaken for evidence of gonorrhea.

The psychiatric implications of the presence of foreign bodies in the urethra and bladder depend on the circumstances. It may be simply a manifestation of immature erotic experimentation; or it may be associated with some kind of sexual fetishism or ritual. It is sometimes seen in psychotic patients. Constriction or strangulation of the penis by a string or a band of rubber, wood, or metal may occur under similar circumstances. It does not necessarily imply serious psychopathology, although it is sometimes observed in psychotic patients Occasionally, a psychotic individual may attempt to castrate himself.

Anxiety about the size of the penis is a frequent manifestation of strong feelings of inferiority in both adolescents and adults. Severe inferiority feelings are rather common and may be associated with a variety of psychiatric syndromes. If the penis actually is undersized, it may be significant of some organic endocrine problem. On the other hand, relative smallness of the penis seldom worries an otherwise normal man because of the truth of the old saying, "It's not the size, but the technique that matters."

Parents who are unnecessarily anxious about their children's genitals usually are expressing a projection of their concern about their own. An attempt should be made to elicit such a history in those cases.

The genital area, in men and in women, is invested with a profound emotional significance. In a rather important way, it symbolizes the individual's capacity for mature behavior in our society. The term, potent refers not only to sexual capacity and fertility but to strength in general, as is indicated by our use of the term, potency, in relation to drugs and medications. Therefore, many individuals interpret damage or threat of damage to their genitalia as a direct threat *to their ability to perform as adults in their community. This is particularly* true of very immature individuals who need to constantly exaggerate their sexual and athletic prowess so as to reassure themselves that they are "big boys" now. A few words of re-assurance, a relaxed, unhurried, sympathetic, professional manner, and a careful, gentle approach are understandably necessary. If an individual appears extremely tense, for example, a young adult coming for a circumcision, it might be very useful to chat with him for a few minutes about his feelings and anxieties so that he needn't feel ashamed of them, nor feel that he is a "sissy".

When the urologist observes symptoms of psychiatric disorders in a patient, it is a matter of great importance to know whether psychiatric treatments are necessary. Generally speaking, if the patient appears unduly anxious, depressed or bizarre, it is best to refer him to a psychiatrist. On the other hand, for the less severe anxieties and tensions of every day living, the urologist himself can give simple psychotherapy by recommending various forms of recreation, such as a vacation, church activities, social activities, sports or hobbies, and there is great likelihood that this will be helpful.

Whenever the urologist believes that there is an important psychiatric aspect in the clinical problem presented to him, it is useful for him to inquire of the patient how he feels about himself in relation to other persons: Is he nervous, tense, upset, irritable, moody, anxious, aggressive, passive, dependent, etc. Sometimes this inquiry, in itself, constitutes beneficial therapy.

If the patient experiences no relief or clarification from an inquiry into his emotional state, and no relief from any of the recreational or social activities suggested, the urologist should not pursue his investigation further. He should refer the patient to a psychiatrist. He can, however, continue to be psychotherapeutic by his confident, respectful and serious interest in what the patient has to say about himself and by an attitude of genuine optimism regarding the course of the patient's illness. Fortunately, many patients have such a powerful inherent drive towards mental health that respect, confidence, and support, patiently given, will provide enough impetus to enable them to achieve healthier living.

SUMMARY

Symptoms common both to psychiatric disorders and organic genito-urinary disease have been listed and their possible significance considered. Simple psychiatric methods have been described which the urologist can employ in suitable patients to supplement urological procedures.

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CYSTOSCOPIC SAFETY: A STUDY OF TOPICAL ANESTHESIA IN DIAGNOSTIC UROLOGY

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During the past 6 years, the urology service of The Long Island College Hospital has seen 2 deaths from the intra-urethral instillation of synthetic, cocaine-like, topical anesthetics. The alarming suddenness with which these catastrophes occurred was our mandate to study the underlying causes and possible remedies for these reactions. The urologist who makes use of topical anesthesia must be prepared to recognize and treat reactions which may occur in spite of his efforts to avoid them.

Aside from admonitions by the Council on Pharmacy of the American Medical Association and an article by Randall in 1923, the literature on this subject is very sparse. Articles in more general terms give equally little information. In 1951 we sent a questionnaire covering all aspects of cystoscopic anesthesia to 171 chief residents serving approved urologic residencies throughout the United States. We are gratified to receive 54 satisfactory replies which, when combined, represented 58,500 institutional cystoscopies a year. Our purpose is to present the results of this study and to discuss the nature, prevention, and treatment of these reactions.

RESULTS OF THE QUESTIONNAIRE

When asked for their preference of technique for routine cystoscopic use, 54 per cent (twenty-nine) of the questionnaires were returned by institutions favoring some sort of topical intra-urethral anesthetic. This was the largest group. It could not be determined whether this great preponderance represents tenaciousness to established methods, or rather is indicative of the need for economy in diagnosis. We believe that for cystoscopy, topical anesthetics have their own merit far above other forms of anesthesia, and this high statistic is recognition of this fact by urologists in general. Within this group, "no anesthesia" was given as second choice (83 per cent), and pentothal was third choice (17 per cent).

Twenty-six per cent (fifteen) replies said that they did not use any anesthesia at all. Many were very specific in their contention that careful, well lubricated instrumentation made the use of any anesthetic unnecessary. These replies also added that they did not hesitate to use anesthesia in some form when indicated. Here topical anesthesia was favored slightly as the second choice of this group.

Third were those favoring intravenous pentothal alone or combined with general anesthesia. These comprised 13 per cent (seven) of the replies. Finally, spinal and caudal were used to the exclusion of other forms of anesthesia by 7 per cent (four) of the hospitals questioned. Any hospital using one type of anes-

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thesia in more than 50 per cent of its cystoscopies was counted as preferring that type. Second and third choices of anesthesia were also covered in the questionnaire, but revealed little of significance, except as noted.

Thirteen different anesthetic agents were cited in the replies received. Metycaine (piperocaine) was the most frequently named (35 per cent). Although this product is not used at the Long Island College Hospital, one of us (F. L. S.) has used metycaine in his office for a number of years with satisfactory results. Nupercaine (dibucaine) (12 per cent), Intracaine (12 per cent), procaine (8 per cent) and cocaine (8 per cent) were next most frequently used drugs. Eight other drugs comprised the remaining 25 per cent. We were surprised that only one reply came from a service which used pontocaine, since this is the drug we have found to be most satisfactory and that we employ routinely.*

Preparation, vehicles, sterilization, and mode of application were covered in the questionnaire. Water was the preferred vehicle (78 per cent), although jelly (20 per cent) and crystals (2 per cent) were used by some. Autoclaving of the solution was done by most services. Eighty-seven per cent of the questionnaires stated that the average instilled volume was between 10 and 30 cubic centimeters of liquid. Methods preferred for instillation were varied. The following figures were obtained for males: bulb syringe (82 per cent), catheter (6 per cent), metal instillator (4 per cent), other (8 per cent). Also in the male, 66 per cent sought anesthesia of both the urethra and trigone. The remaining 34 per cent anesthetized the anterior urethra only. In the female: bulb syringe (35 per cent), catheter (16½ per cent), metal instillator (10½ per cent), cotton pledget (alone) (31 per cent), and other (6 per cent). Most operators seemed satisfied with their method; the average onset of anesthesia was 5 minutes, the average duration thirty minutes.

A large portion of the questionnaire was devoted to toxic reactions. In all, twenty-six were reported, including seven of our own. Of these twenty-six, twelve were mild reactions which responded to simple treatment, eight were severe but responded to treatment, and six resulted in death in spite of intensive treatment. Nine different agents were involved, varying from such agents of low toxicity as procaine and metycaine, to more toxic cocaine, nupercaine, and pontocaine. Twelve patients had previous bleeding from the genito-urinary tract, and seven previous instrumentation. All twenty-six reactions were in males, nineteen of which had either prostatic or urethral disease. Most reactions fitted into the categories laid down (Mayer in 1924 and subsequently the Council of Pharmacy in the *Journal of the American Medical Association*) as contraindications to intra-urethral anesthesia. A few reactions were noted in patients in whom no strictures, previous instrumentation, acute urethral inflammation, or lower tract bleeding could be demonstrated. Five reactions were in dark skinned patients (Negro 3, Puerto Rican 1, Pakhistani 1), partially reviving our earlier belief that these individuals are prone to reactions. Another important common denominator was apparent; this was the mode of application of the drug. In twenty-four of the twenty-six reactions (in two information was lacking) the bulb syringe had been used. This has led us to revise our opinions and technique of application.

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* Metycaine®, Lilly; Nupercaine®, Ciba; Intracaine®, Squibb; Pontocaine®, Winthrop-Stearns.

Most replies showed that patients were given pre-cystoscopic medication, and that the operators had some definite ideas concerning the treatment of reactions. Only a few indicated that they understood that there are different types of reactions, requiring diagnosis and different forms of treatment. Consequently most questionnaires produced replies advocating either inadequate or incorrect emergency treatment. In analyzing our own cases along with those of others, it was not difficult to conclude that reactions could have been avoided and deaths prevented.

THE PHARMACOLOGY OF TOPICAL URETHRAL ANESTHETICS

The preparation of this portion was materially helped by the appearance of an article by Sadove, et al. from which information has been liberally borrowed, and to which the reader is referred.

At present, the synthetic, cocaine-like drugs are still most satisfactory for topical anesthesia. Early workers realized that the toxicity of different drugs does not increase proportionately with their effectiveness. This quality is the main incentive for continued research, in the hope that new compounds with higher margins of safety, minimal local irritation, and greater stability under sterilization can be found. Procaine is accepted as least toxic of these drugs, metycaine is only slightly more so. In clinical use, we have found that nupercaine and pontocaine are the most effective drugs available. We feel that pontocaine, especially, can be used in greater dilutions with a marked diminution of toxicity. This has led to the adoption of pontocaine by our service, employing it with caution as we describe below.

Replies to the questionnaire showed that nearly all operators employ a quantity of topical drug which, if totally absorbed into the blood stream, would produce toxic manifestations. The normal urethral mucosa probably absorbs small quantities of drug. This can be increased manifold when the mucosa is no longer intact from inflammation, instrumentation, or from the forcible injection of the drug with a bulb syringe. In this connection, Dr. Albert J. Paquin of the New York Hospital kindly made available for our inspection three sets of urethrograms showing spread of radio-opaque medium into the veins of the penis, and prostatic and vesical plexi. These were made by the forcible intraurethral injection of intravenous medium with a syringe. Selected patients who had urethral bleeding from instrumentation were used. Up to forty-eight hours elapsed after bleeding had stopped before this was done. We use an aqueous solution for urethrograms routinely, very often taking exposures while pressure is being maintained in the urethra with the medium, and have never obtained such pictures on large numbers of unselected cases. We believe that Dr. Paquin has effectively proved that instrumentation, especially with bleeding, will give direct access to the blood stream. Toxic reactions are the result of the presence of a high concentration of drug in the blood stream. While it is estimated that the normal liver can detoxify a lethal dose in less than sixty minutes, reactions occur in much less time One must use the least amount of drug which will give the desired results in selected, premedicated patients

Most reactions manifest themselves as stimulation of the cerebral cortex and the medulla Apprehension, restlessness, sudden talkativeness, choreiform movements are important early signs Tremors and clonic convulsions are later, more serious signs Also, from stimulation one may see increased respirations, tachycardia, and vomiting Treatment of this type of reaction is best accomplished by short acting barbiturates intravenously, in sufficient quantities to control symptoms Oxygen is important to combat the hypoxia which may result from impairment of the respiratory muscles in convulsions It is also known to increase tolerance of these drugs in experimental animals

The period of stimulation may be brief In these cases depression of the central nervous system may ensue If stimulation is more prolonged, depression may be concurrent with it In such cases of simultaneous stimulation of some centers and depression of others, an exact diagnosis can be very difficult The physician must be prepared to decide accurately and act rapidly to prevent death

Sudden loss of speech is a very important warning sign of early central nervous system depression This may be followed by unconsciousness, flaccidity, and ultimately, respiratory and circulatory failure Supportive treatment until the agent is detoxified offers the best hope of saving the patient It must be borne in mind that central nervous system stimulants and certain cardiovascular stimulants which have central effects are strongly contra indicated They will act in the same manner as the offending drug, depressing further the already depressed patient Oxygen, artificial respiration, head down position, heat, intravenous fluids, and circulatory stimulants should provide the necessary support until the patient recovers himself

Circulatory collapse without central nervous system reaction is rare So are allergic responses such as hives, angioneurotic edema, and asthma Allergy is best treated with epinephrine and antihistaminics Sadove maintains that hypersensitivity or idiosyncrasy is rare Although we do not dispute this contention, our experience with Negroes apparently being prone to reactions leads us to suggest that sensitivity may play some part in reactions

DISCUSSION AND OUTLINE OF TECHNIQUES SUGGESTED

Although there are some who would like to see these drugs permanently relegated to limbo, it seems that they are here to stay at least a while longer Topical use of the antihistamine drugs seems promising, but local anesthetics as we know them eliminate discomfort from contact with the instrument and decrease "stretch discomfort" Properly applied, they also anesthetize the floor of the bladder, an important expedient to examination and ureteral catheterization Patient acceptance is also important The layman expects the doctor to do something to ease the discomfort of a procedure which, by reputation, is a fearsome experience Pentothal, spinal and caudal have their indications, but for diagnostic work on a busy urologic service are time consuming, uneconomical to both the operator and the patient, and can be hazardous in themselves. Topical anesthesia can be made safe if handled properly by personnel who understand the problems involved. The following is the method used at our hospital; we feel it combines safety with expediency and yet remains within the capabilities of our trained help.

The prevention of toxic reactions is relatively simple in contrast to the acute emergency. Topical anesthesia is not given to any patient with a history of previous reactions, or who fits into the categories listed by Mayer and others, namely: recent instrumentation, acute inflammatory conditions, history of lower tract bleeding, or stricture. To this list we add those patients who are known to have impaired hepatic function. Another factor in the prevention of reactions is premedication. This is important and so simple that its use should be universal. Barbiturates are known to increase the resistance of animals to lethal doses of topical drugs by three to four times. Ambulatory patients, when accompanied by a responsible person, or who can rest afterwards should be given the benefit of simple oral medication. We recommend nembutal or seconal, 0.1 gm. with two glasses of water one hour before cystoscopy.

Finally, careful instillation of the topical drug by trained, calm personnel is absolutely necessary in preventing reactions. After analyzing our reactions, and later those of others, we decided that aside from ignoring the basic contra-indications the bulb syringe was also to be considered as a possible culprit. We have found that most patients will not object to the passage of a small, well lubricated, soft rubber catheter. This catheter passes easily in most routine cases. The bladder is emptied to determine residual urine, and prevent dilution of the drug with bladder urine. Ten cubic centimeters of ½ per cent pontocaine (aqueous) are then instilled into the bladder. A penis clamp is applied, and the catheter slowly withdrawn gently injecting another 5–10 cc into the urethra. No force is used, and with this method no drug is spilled. If any difficulty is encountered in passing the catheter, it is withdrawn and examined for traces of blood. If there are none, then 15 to 20 cc of one-half per cent pontocaine are injected with a bulb syringe. Those who use a syringe must remember not to force the liquid into the urethra in order to overcome the sphincter. Instructing the patient to try to urinate relaxes the sphincter and allows the fluid to flow freely into the bladder. Here too a penis clamp is applied. A ten-minute wait before attempting a cystoscopy is advisable. We make one exception to our rule of never using topical anesthesia on a patient with a contra-indication. We do use catheter instillation of topical pontocaine in passable strictures since we prefer to instrument these patients with local anesthesia whenever possible. On the other hand, should the catheter fail to pass we proceed without anesthesia or resort to pentothal.

Since this method of preparation (which anesthetizes the trigone as well as the entire urethra) has been instituted, no reactions, even mild, have been noted in over 3600 cystoscopies. We feel that optimum anesthesia is being obtained without appreciable slow down, or change in economy.

TABLE 1 *Summary of diagnosis and treatment*

Central Nervous System Stimulation May be—cortical or medullary, or both	Early symptoms are—Apprehension and talkativeness, which may be accompanied by hyperpnea, tremors or vomiting This is followed by—Clonic convulsions, and if untreated, death	Treatment should be—*Active and vigorous* 1 Remove drug 2 *Control symptoms with fast* acting IV barbiturate 3 Do not hesitate to give oxygen 4 Watch for CNS depression
Central Nervous System Depression, may follow or be concurrent with stimulation, (i e some centers will be stimulated at the same time others will be depressed) It may be difficult to make an exact diagnosis	Earliest symptom probably is sudden loss of speech This may be followed by unconsciousness and flaccidity Respiratory and/or circulatory failure may ensue, and lead to death	Treatment here is more *watchful* and supportive, but none the less active 1 Remove drug 2 Carbogen 3 Vascular stimulant with minimal CNS effects in order to avoid depressing the patient further (Vasoxyl 10 mg IV) 4 Trendelenburg 5 IV fluids 6 Warmth 7 Artificial respiration 8 Epinephrine when indicated
Circulatory Collapse	Shock	Same as for CNS depression
Allergy	Hives, asthma, angioneurotic edema	1 Remove drug 2 Epinephrine Antihistamines

THE TREATMENT OF REACTIONS

When faced with a reaction, prompt action is necessary, the interval between onset and death can be but a few precious minutes Our entire staff has been briefed on reporting suggestive symptoms, as well as on their role in the treatment of any emergency which may arise We keep an emergency tray and a suction apparatus in the room for cystoscopy Oxygen, carbogen, and resuscitating apparatus with trained personnel are available in the nearby operating room

Removal of the offending agent should be the first consideration This is best accomplished by releasing the penis clamp and rapidly emptying the bladder by catheterization At the risk of being superfluous, we wish to stress that in the distraction of the moment, the cystoscope sheath may be overlooked as the handiest for this purpose Since diagnosis and treatment are very intimately linked, table 1 has been prepared to avoid repetition and to provide a guide and summary for the reader Oxygen is advisable in all cases, however mild We believe that intravenous sodium amytal is the drug of choice for cases of central nervous system stimulation Until recently we have used propadrine as a circulatory stimulant, and feel it is an excellent drug. There are now available two drugs which are of considerable value as vasopressors without central effects. These are vasoxyl and nor-epinephrine. Vasoxyl is our drug of choice in mild reactions. More desperate situations call for nor-epinephrine.

After-care, rest and careful observation are of the essence. On our service one patient lapsed into convulsions about two hours after being controlled, and required a considerable amount of intravenous barbiturate to again be brought under control. Small doses of barbiturate should be given orally for at least 24 hours.

SUMMARY

The results of a questionnaire showed that in 54 per cent of replies topical anesthesia was preferred for routine diagnostic cystoscopy; 26 per cent favored no anesthesia; 13 per cent preferred intravenous pentothal-general.

Most reactions to topical anesthesia are in males, and seem attributable to application of anesthetic solutions with a bulb syringe. Acute inflammatory conditions of the urethra, lower tract bleeding, strictures, prostatic disease, and patients having had recent instrumentation are most commonly involved.

There are two types of reactions to topical anesthetics: stimulation, and depression of the central nervous system. Confusion in diagnosis may occur when stimulation and depression are concurrent. Treatment is based on correct evaluation (see table).

Proper screening and premedication of patients, along with careful instillation of topical anesthetics using a catheter, will prevent most reactions.

Topical anesthesia in routine work is still best and most economical. Properly applied it can be made safe.

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ROTATING SPECIMEN HOLDER

TATE MASON

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During the postoperative period following removal of the urethral catheter after any type prostatectomy, it is our custom to have the patient void into standard 7-ounce (210 cc) clear glass specimen bottles. The patient is instructed to use one bottle for each voiding, and when he has filled the third bottle to discard the oldest specimen and use its container for that voiding. He continues to discard the oldest specimen and use that bottle for each subsequent voiding.

The advantages of such a program are obvious. The attending surgeon can tell

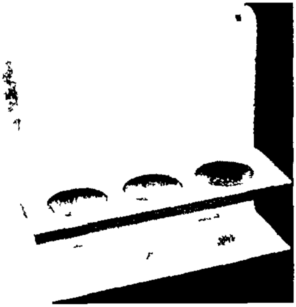

Fig. 1

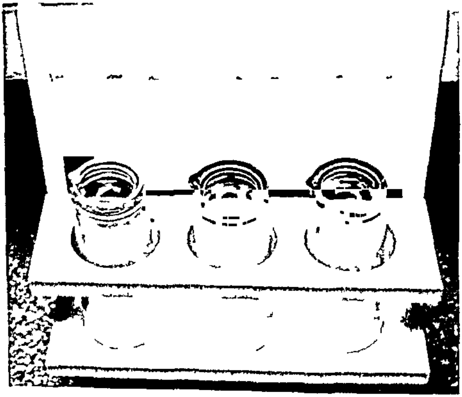

Fig. 2

Accepted for publication January 27, 1954.

at a glance a) how much the patient is voiding each time; b) the approximate amount of bleeding or infection present; and c) should sudden hemorrhage occur after the urine has become clear, he is immediately aware of it.

Until recently, the rotating specimen bottles have been kept on the patient's bedside stand, on the floor, or on the bureau in the patient's room. This has always proved unsatisfactory for obvious reasons. Now a portable holder which is easily accessible to the patient, detachable from the bed, simple, and easily constructed, has been designed. Figures 1 and 2 show the specimen holder and its usual position when in use. It has been found entirely satisfactory and practical.

The author wishes to express his thanks and appreciation to Mr. Brent Mikkelson, engineer at the Virginia Mason Hospital, in Seattle, Washington, who made the original design and models of the rotating specimen holder. These holders are available in quantity direct from the Tower Company, Inc., Seattle 14, Washington.

1115 Terry Ave., Seattle 1, Wash.

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A CONVERTING BRIDGE

CHARLES N. BURNS

The converting bridge herein described is designed to eliminate the passage of two instruments if cystoscopy, urethroscopy or upper tract studies are necessary for the same patient. It permits complete visualization of the bladder with the foroblique as well as the right angle lens system. Thus, better visualization of intravesical and intra-urethral pathologic processes, particularly prostatic lesions, is made possible by this bridge which can be used in the instruments listed below. Also, in the presence of urethral disease, the instrument is useful to facilitate instrumentation. Moreover, visual conversion to the foroblique system is more feasible when mid or lower tract disease necessitates subsequent endoscopic operative procedures. Furthermore, it is designed for ease of production with conventional tools and dyes.

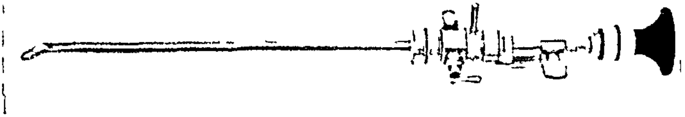

Fig. 1

The instrument (fig. 1) consists of a bridge with a central port, a lock and pegs that adapts a foroblique telescope (68 and 68 A) to the following standard American Cystoscope Makers Inc. sheaths:

A.C.M.I. Cat. No.	*Name*
665	16F Brown Buerger convex sheath
69MF 21	21F Brown Buerger convex sheath
69MF24	24F Brown Buerger convex sheath
175 69	21F Ravich sheath
175 69SP	24F Ravich sheath
210 69	24F McCarthy sheath
213 69	21F McCarthy sheath
196 C	24F Buerger sheath
198 C	21F Buerger sheath

Brilliant illumination may be obtained by using the lamp on the sheath as well as the foroblique lamp. The additional light obviates the dark shadow, or halo, in the distal one third of the field of vision. The illumination achieved is superior to any heretofore obtained. The author has employed this bridge in the 16, 21, and 24 Brown Buerger convex sheaths in over one hundred cases.

Accepted for publication October 13, 1953

In addition, I have used it in other cystoscopes. It permits adequate foroblique vision in all these instruments.

I wish to thank Dr. Peter P. Mayock, 38 N. Franklin St., Wilkes-Barre, Pa., for his advice and clinical material; Dr. Robert C. Jones, Kingsport, Tenn. for suggestions, and Mr. Frederick J. Wallace of American Cystoscope Makers Inc. for the experimental model.

38 N. Franklin St., Wilkes-Barre, Pa.

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A "SURE GRIP" TYPE OF RESECTOSCOPE SHEATH LOCK

GEORGE O BAUMRUCKER

There is an increasing tendency among urologists to perform a more complete prostatic resection by endoscopic means There is also a greater tendency to use counter pressure against the prostate rectally to obtain this end As a result, there has been an increase in the use of the one hand technique of holding the resectoscope, the other hand being used for rectal pressure The friction grip between the sheath and the working element of all resectoscopes on the market was made to separate easily and was designed for the original Stern-McCarthy resectoscope, where no pull was made at this junction Often after a year's use or less, there is a tendency for the prongs to separate and the sheath to disengage from the working element during resection

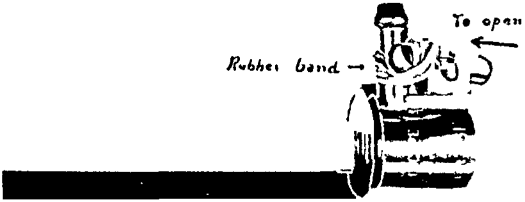

FIG 1

Mr Frederick J Wallace of American Cystoscope Makers, Inc has suggested that substitution of the bayonet lock, as now used on the cystoscope, would solve the problem I believe this would be an excellent modification, but until this comes to pass, the following simple modification (fig 1) will suffice

For the past 6 years I have had success in this respect by using a small rubber band between the water post of the sheath and its spring knob This will hold the working element to the sheath rather than expel it, as is true with the present spring action

SUMMARY

This device holds the sheath against the working element firmly and allows for a one handed technique The sheath can be released from the working element by simply twisting the knob forward

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EXPERIMENTAL UROLITHIASIS IX: INFLUENCE OF INFECTION ON STONE GROWTH IN RATS

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In considering the observations presented in this paper on the relationship existing between infection and urolithiasis, it immediately becomes necessary to distinguish between infection as it may play a role in stone initiation or stone genesis, and infection as it may influence stone growth or continuation. It is quite possible that a distinction of this kind is more artificial than real, but at the present time it would appear to be helpful in achieving a better understanding of the complex interrelations existing between these two conditions and serve to delimit the scope of the experimental observations to be presented here. It is at least conceivable that infection may set the stage, as it were, for the initiation of stone formation, such as by providing nucleus or foreign surface, and thereafter have nothing further to do in influencing the continuation of stone growth upon the initial lesion. On the other hand, a stone may have been initiated quite independently of infection, but when secondary infection now occurred, further growth of stone was greatly enhanced. In this paper we are concerned chiefly with this second mechanism; that is, the role of infection in augmentation of stone growth as distinct from stone initiation.

Since there is almost universal agreement that infection is a very significant factor in stone growth or stone recurrence in the clinical patient, no review of the literature will be attempted. It must be remembered, however, that the relationship between infection and calculus growth seems to be clearly established only when the infecting organism is of the urea-splitting variety. The importance of the urea-splitting faculty of certain organisms in augmenting stone formation has been clearly established by animal experiments, notably by Hagar and Magath,[1] Keyser,[2] Suby and Suby,[3] and Davalos.[4] With urea-splitting infection the consequent alkalinization of the urine and increased ammonia concentration provide a ready and reasonable explanation for stone augmentation by such infection. On the other hand, clear-cut evidence is lacking on the influence of non-urea-splitting infection on stone growth. Some of the effects of both types of infection will be presented here. The role of infection in stone growth can be investigated conveniently by the experimental procedures described in previous

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[1] Hager, B. H. and Magath, T. B.: Etiology of incrusted cystitis with alkaline urine. J. A. M. A., 85: 1352, 1925.

[2] Keyser, L. D.: Studies in urinary calculosis. J. Urol., 54: 194, 1945.

[3] Suby, H. T. and Suby, R. M.: Experimental production of kidney stones with urea-splitting organisms. J. Urol., 57: 995, 1947.

[4] Davalos, H. A., Jr.: The experimental production of stones in the bladder. J. Urol., 49: 639, 1943.

publications of this series[5] where the growth of vesical calculi on foreign bodies was studied in the rat. The foreign body provides the sufficient stimulus for stone initiation. But if infection be introduced at the time the foreign body is inserted, the alterations in stone growth that result from the infection can be determined easily by comparing the amount of stone produced in the infected rats with the amount formed in a control uninfected group. Several experiments of this type have been done using different infecting organisms of both the urea-splitting and non-urea-splitting varieties.

METHODS

As in previous experiments, adult albino laboratory rats were subjected to a suprapubic cystotomy and a foreign body was placed in the urinary bladder to serve as the stimulus to stone formation. In most of the experiments small discs cut from a sheet of zinc were used as the foreign bodies. In one experiment, instead of zinc, the foreign bodies were composed of polythene, a material which previous experiments have shown to be a relatively poor stimulus to stone production. Each experiment consisted of 2 groups of rats, all with bladder foreign bodies. In one group infection was not introduced while in the second group the bladder was infected with the particular organism being studied. This was done simply by contaminating the foreign body with a broth culture just before the foreign body was placed in the bladder.

After the operation the animals were fed our standard rat diet of Purina Fox Chow. Water was available at all times. The experiments were continued for a period of 6 weeks after insertion of the foreign bodies except in one instance where the experiment was terminated in 3 weeks.

To complete the experiment the animals were anesthetized, the bladder again exposed, and urine aspirated for pH determination and culture. Urine culture was made in each instance on a blood agar plate and in Brewer's thioglycolate broth. The bladder was now opened, and the stone removed and weighed. The average stone weight, as given in this paper, was computed from the individual weights of the stones that had formed on the foreign bodies after subtracting the initial weight of the foreign bodies. Accessory "daughter" calculi, when present, were not included in the stone weights. If the urine culture of an animal in one of the control groups was found to be positive, indicating that an accidental infection had occurred, that animal was excluded from the stone weight average. Similarly, all animals were excluded from the experimentally infected groups if they did not yield a pure culture of the organism at the end of the experiment.

Six different organisms were used in these studies. Four of the six: Salmonella enteritidis, 2 strains of Staphylococcus albus, and an organism of the Pasteurella group, were originally picked up from the bladders of rats as accidental infections in previous experiments. The Proteus morganii and B. coli were obtained from the Bacteriology Department of the University of Illinois. Stock cultures of these organisms were preserved in the usual manner and broth cultures were made from the stock cultures 24 hours before they were to be used to produce infection in the rats.

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[5] Vermeulen, C. W., et al.: Experimental urolithiasis I: Development of calculi upon foreign bodies surgically introduced into bladders of rats. J. Urol., 64: 541, 1950.

Mention should be made of the two different rat strains used in this study. It has been shown in a previous paper[6] that the chemical composition of stones produced on foreign bodies in these two strains differs markedly even when the rats are maintained on the same diet. One strain, here called Harlan rats, tends to produce stones of almost pure magnesium ammonium phosphate. This is especially the case in males of this strain. On the other hand, females of the second strain (Holtzman) produce stones that are composed of a calcium phosphate with little or no magnesium. This paper includes observations on the effect of infection on stone formation with both strains using Harlan males and Holtzman females as the test animals.

RESULTS

The experiments have been divided, for convenience, into 3 groups and the results of each group presented by means of a table and a graph. It will be seen that in both the tables and graphs the data obtained from the infected animals of any particular experiment are followed by the results of the corresponding control group of uninfected rats.

The experiments using Proteus morganii as the infecting organism are presented in table 1 and figure 1. This organism is a strong urea-splitter, and it is therefore not surprising that marked stone formation occurred. In 2 of the 3 experiments done with this organism, a ten-fold increase in stone formation was found, while in the third experiment, in Holtzman female rats, the increase in stone due to the infection was approximately seven-fold. The small size of the groups of Harlan male animals is due to the very high mortality that occurs with Proteus infection in these animals. Mortality in the Holtzman females, on the other hand, was not excessive. It will be remembered that "magnesium" stones are produced in Harlan male animals while "calcium" stones are ordinarily produced in Holtzman females. However, in the experiment where Holtzman females were infected with Proteus, the stones changed in composition. In the presence of infection, the stones that formed were composed primarily of magnesium ammonium phosphate, illustrating the tendency toward "magnesium" stone formation in the presence of Proteus infection with its marked change in urinary pH. The pH of the urine of the Proteus-infected rats, as expected, was in all instances higher than the pH of their respective controls.

The second group of experiments is shown in table 2 and figure 2. They were all done with Harlan males which produce "magnesium" stones. The Pasteurella organism, again a strong urea-splitter, produces extraordinary stone growth similar to that seen in the experiments with Proteus; again the average urinary pH was very high in the infected animals. The results obtained with the two strains of staphylococci are particularly interesting. Both of these strains, as will be shown later, are slight urea-splitters, the two strains being equal in this slight

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[6] Vermeulen, C. W. and Goetz, R.: Experimental urolithiasis VII: Role of sex and genetic strain in determining chemical composition of stones in rats. J. Urol., 72: 93, 1954.

TABLE 1. *Stone formation with proteus infection**

Infecting Organism	Strain of Rat	Duration of Exp.	Number of Rats in Group	Aver. pH of Urine	Aver. Weight of Stone in Mg.
Proteus	Harlan ♂	6 wks.	4	7.97	360
Sterile control			5	6.72	39
Proteus	Harlan ♂	3 wks.	5	8.30	120
Sterile control			24	6.86	19.4
Proteus	Holtzman ♀	6 wks.	29	7.43	215
Sterile control			25	6.5	32.2

* All experiments with zinc foreign bodies

ability to split urea. Yet infection with strain 2 is far superior in producing large calculi, with an average stone weight 5 times that of the control group, while strain 1 produced stones but twice the weight of the control. The final experiment shown in table 2 and figure 2 demonstrates the effect of staphylococcus infection (strain 2) when the foreign body consists of polythene rather than our standard zinc. Polythene foreign bodies produced almost no stone in the control animals, presumably because of the nonwetting surface qualities of polythene. But when infection was added, all stone inhibition due to the type of foreign body was lost, and the amount of stone formed was as great as with zinc foreign bodies. Incidentally it may be mentioned that these two strains of staphylococci are tolerated very well by the animals when inserted in the bladder. Excessive mortality did not occur with either of these organisms.

Some curious effects of infection are shown in table 3 and figure 3 where the results with B. coli and S. enteritidis are given. (Some observations on Salmonella infection and stone formation have been reported in a previous paper of this

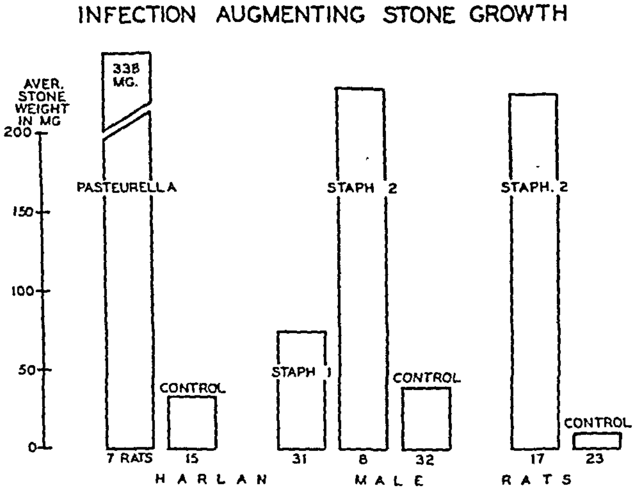

FIG. 1. Graphs of 3 experiments showing average stone growth in rats with zinc foreign bodies in control and infected groups. Size of each group indicated by number below each bar. Second experiment (center) of 3 weeks' duration, other 2 experiments of 6 weeks' duration.

TABLE 2. *Stone formation with Pasteurella or staphylococcus infection**

Infecting Organism	Type of Foreign Body	No of Rats in Group	Aver pH of Urine	Aver Weight of Stone in Mg
Pasteurella	Zinc	7	8.1	388
Sterile control		15	6.6	34.3
Staph. strain 1	Zinc	31	6.62	75
Staph. strain 2		8	7.11	228
Sterile control..		38	6.61	40.2
Staph. strain 2	Polythene	17	7.1	223
Sterile control		23	6.83	10

* All experiments of 6 weeks' duration with Harlan male rats.

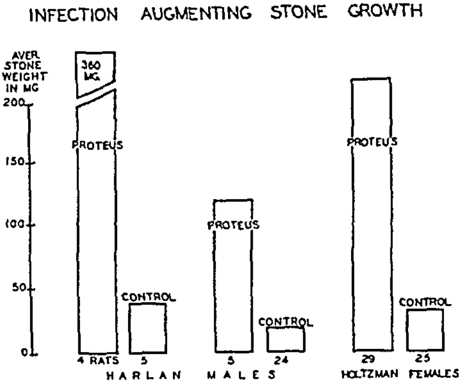

FIG. 2 Graphs of 3 experiments showing average stone growth in control and infected groups of rats. Size of each group indicated by number below each bar In experiment 3 (on the right) polythene foreign bodies used, other 2 experiments with zinc Duration 6 weeks.

series.[7]) Both B. coli and S. enteritidis were found to be well tolerated by the animals. The particular strains of these 2 organisms were completely non-urea-splitting. With the Holtzman female rats, where "calcium" stones were produced, the groups infected with B. coli or S. enteritidis produced stones of somewhat larger size than the controls. Statistical comparison of the results with Salmonella infection versus control indicated that the slightly larger average stone in the Salmonella-infected rats quite possibly may be explained by chance alone, but in the case of B. coli infection the statistical analysis indicated that there is a real difference ($p < 0.01$) in the amount of stone produced, and the conclusion that this infection augments stone formation seems to be justified. On the other hand, with these same infecting organisms stone growth was prac-

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[7] Vermeulen, C. W., et al · Experimental urolithiasis V: Prevention and dissolution of foreign body calculi by infection with Salmonella enteritidis. J. Urol., 68: 790, 1952.

TABLE 3. *Stone formation with B. coli or Salmonella enteritidis infection**

Infecting Organism	Strain of Rat	Number of Rats in Group	Aver. pH of Urine	Aver. Weight of Stone in Mg.
B. Coli	Holtzman ♀	18	6.49	48.1
Sterile control		12	6.4	26.6
S. Enteritidis	Holtzman ♀	44	6.54	39.6
Sterile control		29	6.48	32.9
B. Coli	Harlan ♂	19	6.65	0
Sterile control		22	6.77	42.8
S. Enteritidis	Harlan ♂	73	6.67	2.2
Sterile control		55	6.7	45.4

* All experiments with zinc foreign bodies and of 6 weeks' duration.

tically completely prevented where the tests were done in the Harlan animals which produce stones composed of magnesium ammonium phosphate. There is, then, a sharp difference in response to these infections dependent upon the strain or sex of the animal used. In animals producing "calcium" stones, these infections have either no effect or serve to augment stone growth; while in animals tending to make "magnesium" stones, such infection is strongly inhibitory. Since the numbers of animals in at least some of the different groups are relatively large, there is very little likelihood that these conclusions are in error. The average urinary pH of the infected animals was not appreciably different from that of the controls, and thus there is no possibility that the effect of these infections can be explained by changes in the pH of the urine.

Initial qualitative test for urea-splitting ability on ordinary bacteriologic urease testing media indicated that of the 6 organisms used in this study, only the Proteus and Pasteurella produced the color changes indicative of urea-

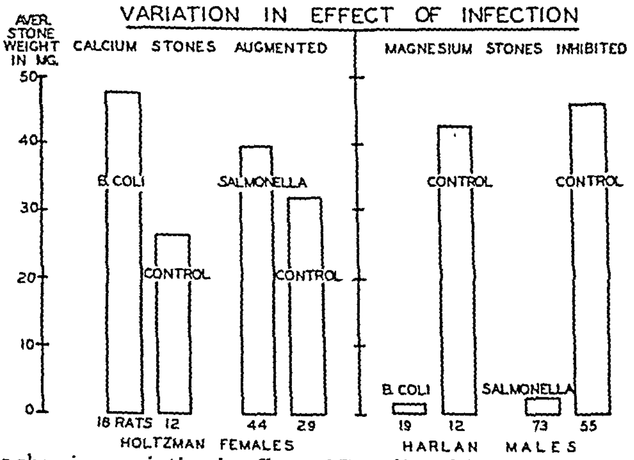

FIG. 3. Graphs showing variation in effect of B. coli and S. enteritidis infections on stone growth on zinc foreign bodies in Holtzman female rats (which produce "calcium" stones) and Harlan males (which produce "magnesium" stones). Size of each group indicated by number below each bar. Duration 6 weeks.

TABLE 4. *Influence of infection on pH and ammonia production using human urine in vitro**

Infecting Organism	Incubation for 4 Hours		Incubation for 24 Hours	
	pH	Ammonia N	pH	Ammonia N
		mg %		mg %
Control (uninfected)	7.18	52.8	6.99	56.0
Proteus morganii	8.97	150.5	9.20	325.0
Staph. 1	7.12	63.0	8.64	126.5
Staph. 2	7.06	60.0	8.60	117.0
Salmonella enteritidis	6.80	56.5	6.72	59.2
B. coli	—	60.0	7.12	60.0

* Tests run after introducing 0.5 cc of a 24 hour Brewer's culture of the respective organisms into 10 cc of sterile human urine.

splitting activity. With the exception of Pasteurella, the organisms were also subjected to quantitative test for their ability to split urea. The results of this test are shown in table 4. The tests were run simultaneously by inoculating 10 cc samples of sterile human urine with 0.5 cc of a 24-hour Brewer's broth culture of the organism. Four hours later the pH and the concentration of ammonia in each tube were determined. Similar examinations were done at the end of the 24 hour period. While the pH and the ammonia content of the sterile control tubes remained essentially the same, the pH of the tubes infected with Proteus, a strong stone augmenter, was very distinctly changed toward the alkaline side, and the concentration of ammonia was 3 times that of the control after 4 hours of incubation. On the other hand, the 2 strains of staphylococci had no significant effect on pH or ammonia concentration at the end of 4 hours. At the end of 24 hours there were definite evidences of urea splitting, but it will be remembered that a very heavy inoculum had been used, and that though both strains exhibited equal powers for urea splitting, strain 2 was far more potent as to stone formation. The last two infections studied, B. coli and Salmonella enteritidis, were shown by this test to be completely non-urea splitting.

DISCUSSION

Because of the nature of these experiments using foreign bodies, our concern is primarily with the effect of infection on continuing stone growth rather than with stone initiation. The introduction of the foreign body already provides conditions suitable for the initial formation of the stone. The experiments are therefore interpreted as a demonstration of the various possible effects of infection on continuing stone growth or progression.

The very rapid stone growth that occurred with Proteus and Pasteurella infection illustrates the well known effect of urea-splitting infections in producing calculus augmentation. It seems clear that this is due, in large part at least, to the alkalinization of the urine and increased ammonia concentration. The results obtained with Proteus infection in the Holtzman female rats are interesting as an illustration of the tendency of urea splitting infection to result in stones composed of magnesium ammonium phosphate. Whereas the uninfected controls

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XANTHINE CALCULI OF THE KIDNEY

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As Bergman (1948), Butt and Halliman (1944), Gersh and Meltzer (1946), Kretschmer (1937) and Pearlman (1950) have noted, urinary xanthine calculi are very rare. They collected 23 cases (9 bladder, 5 kidney, 3 ureter, 1 urethra and 5 site unknown).

In the Japanese literature there are 4 reports of this disease: Kondo's case of 25 year old woman who had left renal xanthine calculus (1927); Higaki's case of a 72 year old man with an impacted stone in a urethral fistula (1940); Nishi's case of a 61 year old man with a bladder stone (1950); and Ito's case of 5 year old boy with a bladder stone (1951). I would like to add the following case to the literature.

CASE REPORT

A man aged 44 with symptomless, daily hematuria, which occurred in February 1952, was seen in the Tokyo University out-patient clinic on April 11 and was hospitalized May 2, with a diagnosis of essential hematuria.

General examination was not remarkable. Blood studies were normal. Cystoscopy revealed only bleeding from the left ureteral orifice. Chromo-ureteroscopy (indigo carmine) was more concentrated on left side; dye appeared from the right side in 7 minutes and 40 seconds and from the left in 4 minutes and 25 seconds.

A plain urogram showed no opaque shadows. Excretory urography revealed only slight dilatation of the right renal pelvis (fig. 1, *A*). The retrograde pyelogram combined with perirenal air insufflation on the left side (fig. 1, *B*), and aortography (fig. 1, *C*) failed to reveal the cause of bleeding. The diagnosis was essential renal hematuria, and various hemostyptics were given without benefit. Because of persistent bleeding a left nephrectomy was done. The kidney appeared grossly normal, but on palpation the parenchyma was studded with numerous small nodules.

The pathologic specimen measured 10 by 5 by 4 cm. and weighed 130 gm. (fig. 2, *A*).

On the cut surface (fig. 2, *B*), there were many small holes, in which fine granular concrements were found. These were brownish, rounded or oval, smooth and friable; chemically they were pure xanthine.

These concrements sectioned easily with the parenchyma (fig. 3). Microscopically (low power) many small cystic structures were seen in the parenchyma, whose diameter varied between 1 and 5 mm. The contents stained quite homogeneously with eosin.

The interior of these cystic structures was almost covered with flat or cuboidal epithelium, but many were partially denuded and showed evidence of hemorrhage (fig. 4, *A*).

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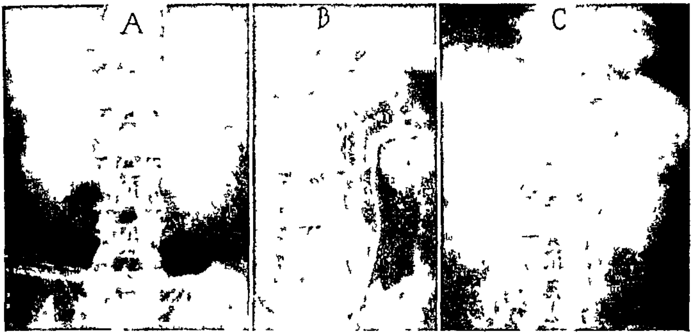

Fig. 1

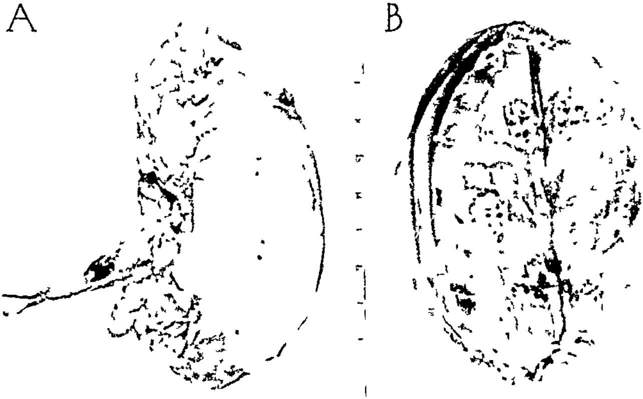

Fig. 2

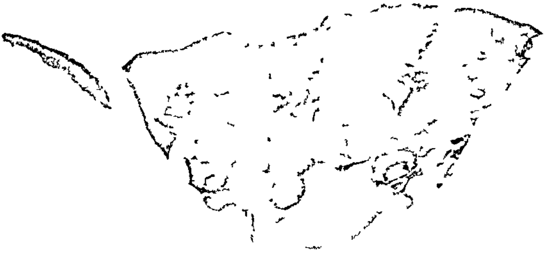

Fig. 3

cision of calyceal diverticula have been reported. To these we now add two additional cases treated successfully in this manner.

CASE REPORTS

Case 1. E. S., Reg. No. 210903, a 30 year old white man, was admitted with a history of chills and fever for 4 days prior to admission. Past history revealed anorexia, gastro-intestinal cramps, and right costovertebral angle pain intermittently for the past year. A gastro-intestinal series in June 1950 was negative. The patient was seen by a civilian urologist in April 1951, and a diagnosis of solitary intrarenal cyst made. He was transferred to our care for disposition and treatment.

On admission, the temperature was 102F orally, and the blood pressure 120/65. Physical examination, including rectal examination, was negative except for right costovertebral angle tenderness extending to the right hypochondrium. Urine cultures developed moderate growth of Pseudomonas aeruginosa and Staphylococcus aureus. The patient was placed on antibiotics and the temperature returned to normal in 48 hours. Tenderness persisted in the right costovertebral angle. Cystoscopy and retrograde pyelography revealed a 3 cm. diverticulum of the superior calyx of the right kidney (fig. 1, *A*) which retained the dye on delayed films. The remainder of the laboratory studies were normal. On July 5, 1951 the patient was operated on and through the routine lumbar incision, enucleation of the diverticulum was done with primary closure of the wound without nephrostomy drainage. The postoperative course was uneventful, and the patient was discharged on sick leave on the eighth postoperative day. One month later, urograms revealed normal right renal architecture (fig. 1, *B*). The patient was symptom-free.

Case 2. J. B. Reg. No. 232079, a 37 year old man, complained of constant dull aching in the left flank and costovertebral angle of 5 months' duration. Past history revealed an episode of left ureteral colic in 1948, with passage of

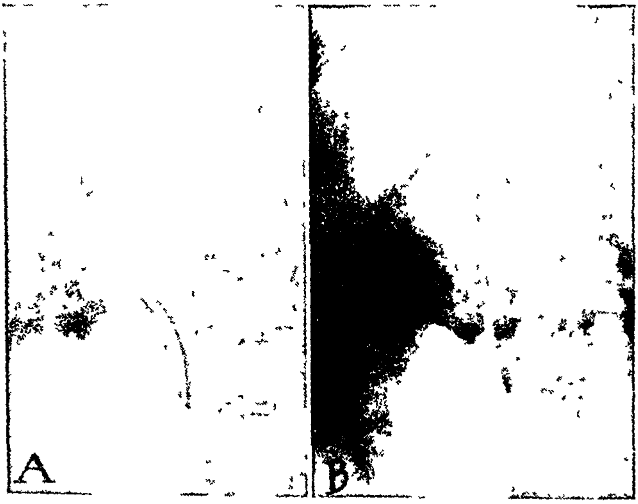

FIG. 1

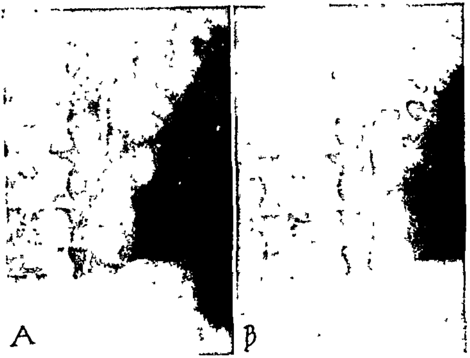

FIG. 2

a urinary calculus shortly thereafter. The remainder of the history was essentially negative. On admission the temperature was 98.6F orally and the blood pressure 106/68. Physical examination including rectal examination was normal throughout. Routine admission laboratory tests were normal as were repeated urine examinations. An excretory urogram revealed a 2 cm. oblong diverticulum of the middle minor calyx of the left kidney (fig. 2, *A*). Following the usual preoperative preparation, the left kidney was exposed and the intraparenchymal diverticulum enucleated with primary closure of the wound. The postoperative course was complicated by the moderate intestinal ileus which was relieved by Wangensteen suction. The patient was discharged on sick leave the fourteenth postoperative day. Retrograde urograms were made 6 weeks postoperatively and showed normal left renal architecture (fig. 2, *B*). The patient was completely asymptomatic and the wound well healed.

DISCUSSION

Two cases have been presented which illustrate the entity known as calyceal diverticulum. Whether these formations are due to previous papillary trauma due to calculi cannot be definitely stated, but in one case there is a definite history of a previous homolateral calculus.

Both cases were treated surgically by conservative measures aimed at conserving all possible normal renal parenchyma. No urinary drainage tubes were used in either case, the kidney being closed primarily. The final results in both cases were excellent as evidenced by follow-up examination and postoperative pyelograms.

SUMMARY

A discussion of the theories of etiology of calyceal diverticula is given.

Two cases are reported in which the diagnosis of calyceal diverticulum was made preoperatively. The patients were treated by conservative surgical methods and postoperative results have been excellent.

It is hoped that calyceal diverticulum will become a recognized entity and that conservative surgical methods be followed in its future treatment.

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RADICAL SURGERY IN RENAL NEOPLASMS

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The statistical 5-year cure rates in renal carcinoma leave much to be desired. These results, varying between 16 and 20 per cent in various reported series, have stimulated many of us to find a way to improve the results of surgery in renal carcinoma. This attempt has been made not only with early diagnostic criteria but also relative to the surgery of those cases which are apparently operable and without evidence of distant metastasis. Early diagnosis is difficult in most renal tumors, especially those which do not cause bleeding until late in the disease (this occurs in approximately 30 per cent of the cases). The failure on the part of the urological surgeon to be able to cure a tumor which is local at the time of operation has resulted in an extension of the surgical procedure to include the entire perinephric fat and retroperitoneal tissues along with the lymph glands, plus incisions to allow adequate exposure.

While the idea of removing the surrounding tissues in doing nephrectomies is not new, there has been a great impetus given to this recently in the literature in the reports of Foley, Chute and Nagamatsu. The studies of Beare and McDonald relative to the local invasion into the renal capsule and the perinephric fat by renal carcinoma have made it mandatory that any surgical approach be radical. The last named authors pointed out that of 480 cases of renal malignancies, the neoplasm had extended locally beyond the kidney in 343. They found a much lower 5 year survival rate among the cases with renal capsule and perinephric fat involvement than those in which neoplasms were confined within the kidney. Dr. Hugh Young in *Young's Practice of Urology* made the suggestion that as much perinephric fat as possible be taken with a renal tumor and pointed out the feasibility of removing the entire envelope about the kidney. He did note, however, the difficulty of exposing the renal pedicle with this procedure.

Other men (Stevens, Vivian, Judd and Hand, Mathé, and Cahill) have advocated removing as much fat as possible along with lymph glands and perinephric tissue *en masse*. Sweetser devised an abdominal flap incision to allow better exposure and earlier ligation of the renal pedicle. Chute advocates the use of the thoraco abdominal approach with complete block removal of the perinephric tissues, lymph glands and tumor. In order to avoid entering the chest, the recent contribution of Nagamatsu with his dorsal-lumbar flap incision has added an excellent approach to carry out this radical procedure. Dr. Richard Chute in discussing Dr. Nagamatsu's paper in Boston in 1951 stated, "I am sure that there must also be many surgeons who are not doing this partly because they have not realized the importance of so doing and partly because just how to go about it has not been called to their attention." This radical

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Read at annual meeting, Northeastern Section of American Urological Association, Shawnee on Delaware, Pa., September 15-18, 1953.

approach has been further extended in some instances by ligation of the inferior vena cava below the left renal vein and resection of that part involved by tumor as well as opening the vena cava and removing tumor emboli.

There is no place in the surgery of renal tumors today for the manual extraction of a kidney through Gerota's fascia. This results in tearing of lymph vessels and veins and undoubtedly in many instances, tissue already involved with tumor. Radical nephrectomy is an easier, less shocking procedure, and entails less blood loss than one carried out within Gerota's fascia. We wish to present the following case in point.

CASE REPORT

Mr. J. C., R.G.H. No. 19152, was first seen in consultation in another hospital in this city on May 6, 1952. The patient had been admitted for terminal care due to an advanced carcinoma of the kidney. His history dated back to May 1951 at which time gross hematuria had developed. In September 1951 retrograde studies were carried out and revealed a large renal tumor on the right side (fig. 1). The left kidney was normal. Nephrectomy was attempted inside Gerota's fascia through a flank incision after resection of the twelfth rib. Apparently severe bleeding was encountered. Tremendously enlarged veins coursed about the entire tumor. With the kidney still in place, clamps were placed in the region of the renal pedicle, left on, and the wound closed about

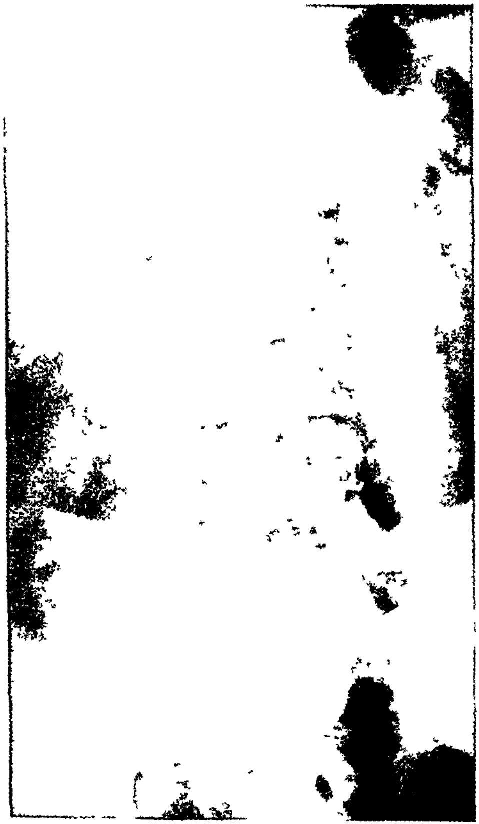

FIG. 1 Retrograde pyelogram (September 1951) revealed large tumor of right kidney.

these. The patient's family and physician were told that the tumor was inoperable. After a stormy postoperative course, the patient recovered. He received deep x-ray therapy to the tumor in the fall of that year. His course was gradually downhill and he was re-admitted to that hospital on May 1, 1952 critically ill with chills and fever ranging up to 104F. A fungating, foul smelling mass was present in the wound which discharged pus and fluid. Nausea and vomiting occurred frequently throughout the day and he was irrational at times. Laboratory investigation revealed marked anemia with 8 gm. hemoglobin. It was at this time that he was seen in consultation. On physical examination he was a desperately ill white man showing evidence of recent weight loss. He answered questions poorly and his memory for recent events was not accurate.

The local examination revealed a right flank incision in the center of which a fungating, foul mass was present covered with pus and blood. A huge mass was present in the flank extending down to the region of the iliac crest across the midline and up under the rib-cage. This mass, although fixed to the abdominal wall, was slightly movable and could be ballotted. Metastatic survey failed to reveal the evidence of any distant metastasis. It was felt that there might be a remote chance of removing this growth. He was started on daily blood transfusions, parenteral vitamins, intravenous fluids and antibiotics. On June 3, 1952, he was transferred to the Rochester General Hospital. At that time he appeared more lethargic. His blood pressure was 110/80; pulse 110; respirations 22; temperature 103F. The local physical examination was as before. Laboratory examination: erythrocytes, 4.99 million per cc; hemoglobin, 13.5 gm.; color index, .96; leukocytes, 25,800 per cc; differential, polymorphonuclears 44 per cent, segments 50 per cent, eosinophils 2 per cent, lymphocytes 3 per cent and monocytes 1 per cent. Urine: albumin, trace; sugar, negative; white blood cells, rare; erythrocytes, absent; casts, abundant. Blood chemistries: chlorides, 623 mg. per cent; nonprotein nitrogen, 50 mg. per cent; total proteins, 6.0 gm. per cent; albumin, 2.7 gm. per cent; globulin, 3.3 gm. per cent; hematocrit, 39 gm. per cent; sodium, 135 m/Eq; potassium, 5.1 m/Eq An electrocardiogram revealed sinus tachycardia. Blood volume studies were essentially normal.

Two days before operation copious amounts of fecal matter began to drain through the fistulous opening. Barium enema and injection of opaque material into the fistula failed to reveal any connection with the large or small intestine. On June 7, 1952, operation was carried out with resection of the terminal ileum, cecum, ascending and part of transverse colon, along with the entire retroperitoneal tissues, kidney and the abdominal wall invaded by tumor *en masse* (fig. 2).

Pathological diagnosis: Anaplastic hypernephroid carcinoma of the right kidney. It invaded the cecum and abdominal wall and had produced a fistula from the cecum and kidney to the abdominal wall.

Postoperative course: The patient's postoperative course was complicated and difficult. Marked oliguria, recurrent shock-like episodes apparently due to hypokalemia, disturbances in the electrolytes and fluid balance, uremia, jaundice, anemia, wound infection and marked intestinal distention occurred. He was treated with antibiotics, adrenal cortical extract, cortisone, Wangensteen suc-

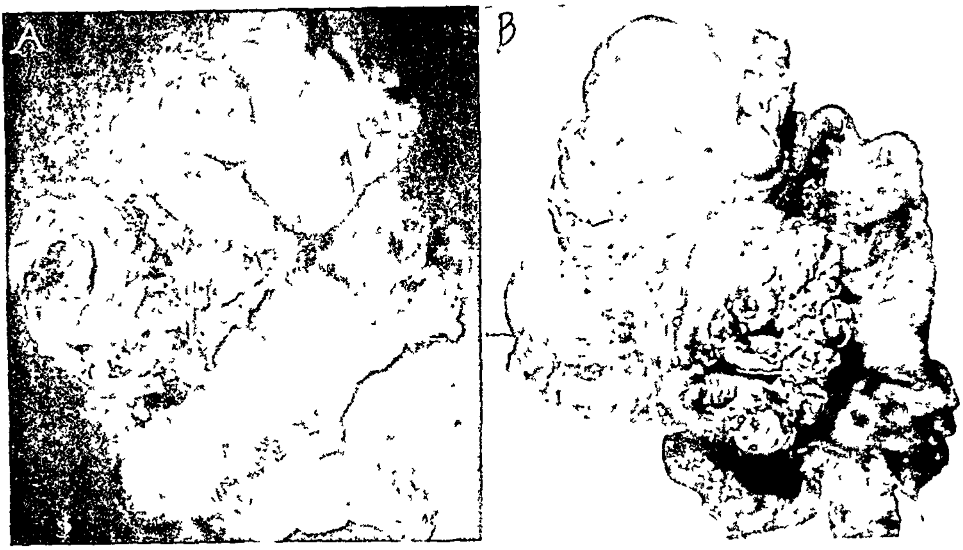

FIG 2 *A*, entire specimen removed shows bowel attached to large renal mass and tumor growing through abdominal wall *B*, probe is in fistulous tract which passed from cecum through kidney to abdominal wall.

tion, prostigmine, tube feedings, blood and electrolyte solutions as determined by daily or more frequent chemistries. The nonprotein nitrogen rose to 165 mg. per cent on his ninth postoperative day. His condition was precarious for the first 2 weeks postoperatively but following this he began to make slight but gradual improvement. On his seventeenth postoperative day the Wangensteen suction was discontinued. Severe mental depression occurred. It was decided that familiar surroundings would be more helpful in his recovery. On his twenty-fifth postoperative day, he was allowed to be up for a few minutes. The following day he was discharged home. At the time of discharge his nonprotein nitrogen was 95 mg. per cent and his white blood count was 18,100. The remainder of his chemistries were approaching normal limits.

He was re-admitted on two separate occasions with abdominal pain, nausea and vomiting. On the first admission, a bile cyst of the liver was drained. On the second, he responded to Wangensteen suction. The icteric index was elevated both times but returned toward normal. Both attacks had been preceded by large meals. It was felt that in mobilizing the duodenum and bile ducts some distortion of this area occurred which was accentuated by a full stomach. He was started on small feedings at frequent intervals. Since that time his progress has been most satisfactory and without recurrence of these episodes. Complete metastatic survey carried out in January 1953 and June 1953 have failed to reveal any evidence of any metastasis. At the time of our presentation the patient is 15 months postoperative without evidence of recurrence and leading a normal existence. His general health is excellent.

DISCUSSION

Consideration of any radical procedure is frequently frought with the difficulties of prolonged and extensive surgery, long hours of tedious postoperative care and the heartaches and headaches that go with these serious problems and poor-risk patients. Certainly any practicing physician must give to the patient every chance for survival that is available. Radical procedures have wended their way into many of the operations carried out in Urology in an attempt to improve the results obtained. Certainly surgery in cases of tumor in which the kidney is skinned out or a small amount of perirenal fat is included in the dissection, is inadequate in approximately 50 per cent of the cases. Many tumors which have been previously called inoperable in the past undoubtedly would have been operable if 1) adequate exposure had been obtained at the time of surgery, and 2) a radical attempt had been made to remove the tumor. Extensive hemorrhage is a matter usually of poor technique, roughness, or inadvertent entering of a large blood vessel through an incision which makes adequate visualization and mobilization impossible. The additional time required for adequate exposure is a necessary component of the radical procedure. Certainly the operator with good exposure can work better, quicker and with less danger than one who is trying to do the same job relatively blindly. If a proper approach is taken, there will be fewer inoperable tumors. Even these, with distant metastases, if they are isolated and single, should have the benefit of surgery. In considering extension of a tumor into the renal vein or the veins surrounding the kidney, one must remember two facts: 1) that all the metastatic cells which are released from the tumor site are not viable; and 2) that those which are viable do not necessarily fall upon fertile soil.

There have been many objections to radical surgery in several fields especially those of tumor involving the lower pelvic region in which a wet colostomy is the end result. Unfortunately, these people judge the result relative to themselves as normal individuals. Certainly a wet colostomy is a much more tolerable condition than a vesical, vaginal, rectal fistula with a stinking, foul mass of feces and urine draining per vaginum. This situation, however, is not true nor is to be considered in relation to radical surgery of the kidney. In no way is an individual forced to accept a condition which is not within the normal limits of his previous life.

In considering the case presented of a man who had been labeled an inoperable case of carcinoma of the kidney and who had been sent in for terminal care, we were impressed by the extent of the local growth of this tumor which is most unusual in carcinoma of the kidney. The x-ray therapy may have been a factor in retarding dissemination of the tumor. Unfortunately, the decision to label this individual inoperable was based upon extensive hemorrhage which the

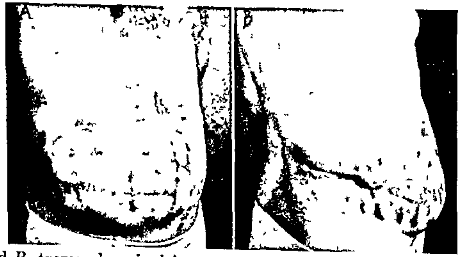

FIG. 3. *A* and *B*, tremendous incision necessary to perform procedure is shown. *B*, one can note incisional hernia present. Only tissue used here for closure was skin.

operator encountered in an attempt to do a conservative nephrectomy. This then becomes an inoperable case as in many instances, based not upon the true situation of the tumor but upon the judgement of the operator. This man has in no way been made a physiological cripple. He has been returned to normal, physiologically speaking except for a large incisional hernia (fig. 3).

Renal colic fistulas due to stone, tuberculosis, and infection have been recorded in the literature. The occurrence of a renal colic fistula due to carcinoma of the kidney has not been reported to our knowledge. Wesson was unable to find any instance in the literature up to 1938. None has been reported since that time. In discussing the subject of fistulas of the kidney, Ratliff stated that in all cases the primary etiology lies in the kidney rather than the bowel. The possibility that trauma at the time of the first operation is a factor in the breaking down of the peritoneal barrier must be considered.

SUMMARY

Radical nephrectomy is the only surgically sound operative procedure in malignancy of the renal paranchyma.

The instances of operability will be increased with adequate exposure.

In the case presented a tumor judged inoperable became operable by adequate exposure and radical excision, and a renal-colic fistula due to carcinoma of the kidney is reported for the first time.

We wish to acknowledge the technical preparation of lantern slides and photographs from the photograph department by Mr. John Beiter and directed by Dr. Milton Bohrod.

We also wish to acknowledge gratefully the help of Dr. Jörgen Schlegal of the Buswell Urological Research Laboratory (Director, Dr. W. S. Scott) Medical School of the University of Rochester, for both the excellent co-operation of himself and his laboratory in orientation of the problems of electrolyte and fluid balance in this case. The urine pH meter which Dr. Schlegal invented was indispensable in evaluation of the patient's sodium balance.

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HEMANGIOMA OF THE KIDNEY: AN INCIDENTAL FINDING AT AUTOPSY

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Hemangioma of the kidney has been recently reviewed by Butt and Perry, who report a case in which the diagnosis was made before operation. McCrea presented an analysis of 73 cases reported in the literature with a discussion of renal hemangioma. Waterfall reported a case of severe hematuria requiring nephrectomy which was found to be due to angioma of the kidney. The English literature refers to the lesion as angioma whereas in the American literature we refer to it as hemangioma.

Reports of renal hemangioma in the literature have been those brought to the physicians' attention as urological problems because of gross hematuria. Little or no mention has been made of the incidental finding of this relatively rare lesion other than by Bell who noted one case in 30,000 consecutive autopsies. Rottino and Mohan reported a case found at autopsy but there was a history of hematuria prior to the patient's death. Riley and Swan failed to find a hemangioma in 13,219 autopsies. In 36 tabulated cases only one was an incidental finding at autopsy.

Judd and Simon stated that this type of tumor rarely attains a diameter of more than 1 or 2 cm. and the subsequent case reports have tended to confirm this impression, but larger lesions do occur. Rives and Pool reported a diffuse hemangioma measuring 7 by 5 by 6 cm. Lazarus and Marks in their series of cases reported that the tumor may vary from the size of a pinhead to that of a mass replacing one-third of the kidney parenchyma. A case approximating the latter size has been extremely rare. The case reported here is considered unique because of its incidental finding at autopsy without previous urological symptoms and its unusually large size.

Dukes believed angioma to be a common cause of essential hematuria. Nephrectomies were performed on 9 cases of essential hematuria without clinical or radiological evidence of neoplasm or other disease of the kidney. Each kidney at first appeared to be normal but subsequent dissection revealed 4 cases of renal purpura, hemorrhage in the mucous membrane of the renal pelvis, 3 cases of angioma of renal papillae, in one a minute adenoma and the last a tuberculous ulcer at the apex of a papilla. He concluded that angioma is one of the commonest causes of so called essential hematuria.

CASE REPORT

E. M., a 60 year old white woman, first entered the Jewish Hospital August 6, 1948, with pain in the thoracic spine of 1 month's duration. She was a known diabetic for 3 years, and was treated with insulin and diet. Her only urinary complaint was nocturia 2 to 3 times. Her past history was negative for other urinary

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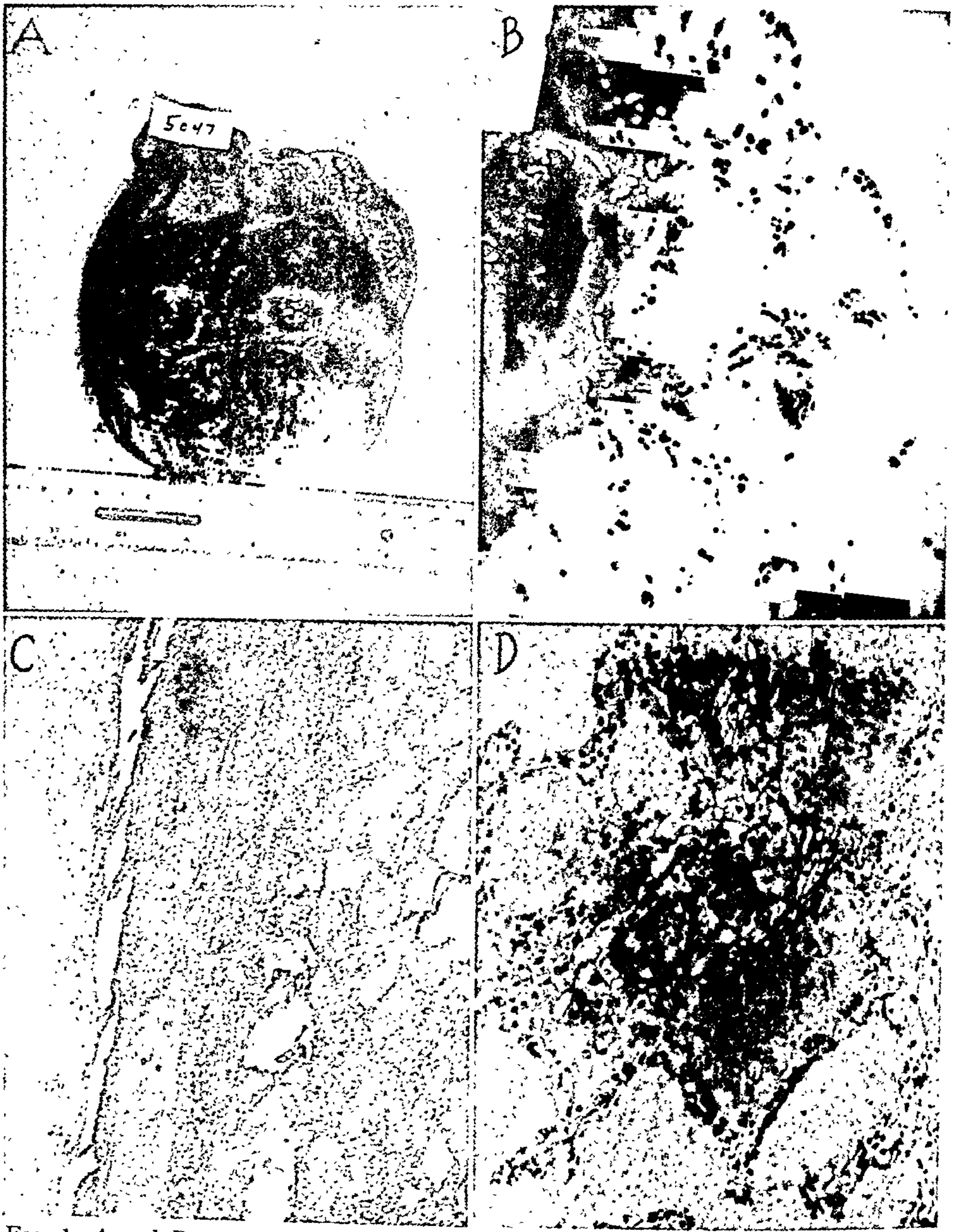

FIG. 1. *A* and *B*, gross specimen. Note large hemorrhagic nodules occupying medulla and pelvis. In *B* small satellite nodules are present in lower right corner. *C* and *D*, large vascular spaces filled with blood and lined by endothelium. Sections are through hemorrhagic nodules.

symptoms. Urinalyses during this admission revealed glycosuria and 1 plus albuminuria, but no hematuria. She was discharged September 17, 1948; x-ray evidence of osteo-arthritis was taken to explain her admission complaint.

The patient was re-admitted October 3, 1948, after being found comatose at home; but shortly after arriving at the hospital she was aroused before any therapy was instituted. Subsequent studies failed to explain the coma. She was in moderate ketosis with a blood sugar of 234 mg. per cent, and therapy was directed toward improving her diabetic status. Her complaint at this time was the same back pain as on her previous admission plus severe pain radiating down both lower extremities. Workup, including lumbar puncture, failed to reveal any additional factors accounting for her pain other than diabetic neuritis. At one time during this admission, the patient's bedpan was found to contain bloody urine, but the blood was assumed to have been vaginal in origin, especially since she was receiving estrogen therapy. Urinalyses showed varying amounts of sugar, a trace to 2 plus albumin, occasionally many leukocytes but only occasional rare red blood cells. She was discharged January 16, 1949.

Her third and final admission was June 9, 1950, on which date she entered in diabetic coma with a blood sugar of 850 mg. per cent and the urinalysis showing 4 plus acetone, 3 plus albumin and 3 per cent sugar. She failed to respond to all therapeutic measures and died 14 hours after admission.

At autopsy the right kidney was normal. The left kidney (fig. 1, *A* and *B*) weighed 270 gm. and measured 15 by 7 by 6 cm. A soft, reddish-brown, friable mass, measuring approximately 12 by 5 by 5 cm., protruded into the hilus when the kidney was bisected. The pelvis of the kidney was compressed by this friable, hemorrhagic tissue which had replaced almost all of the medulla, but which had a sharp margin at the corticomedullary junction. The cortex was slightly compressed but showed a smooth surface when the capsule was stripped.

Microscopic examination (fig. 1, *C* and *D*) showed a thick, hyalin, fibrous capsule surrounding the tumor mass. One area of calcification with bone formation was found, in which a marrow cavity was present. The capsule also separated the tumor from the medulla. In areas where a calyx could be seen, the capsule coursed adjacent to the calyx. The cortex adjacent to the capsule showed many hyalinized glomeruli and thickened, hyalinized small arteries and arterioles. The inner half of the capsule contained many phagocytes filled with hemosiderin pigment. The tumor proper consisted of numerous vascular channels in compact arrangement so as to give a honeycombed appearance. These channels were lined by a single layer of endothelial cells. In some areas the vessels were separated by hyalin septa containing hemosiderin laden phagocytes. In other places fat tissue separated the vessels. Most of the vessels were filled with blood, and some contained thrombi in various stages of organization. Diagnosis: Cavernous hemangioma of the kidney.

DISCUSSION

It is exceedingly difficult to envisage a hemangioma of the kidney attaining the size of our case without causing symptoms, particularly hematuria. One can only speculate in regard to the presence of bloody urine in the patient's bedpan on one occasion during her second admission. If this was true hematuria, and it is very questionable, it was the only occasion on which one could have suspected a tumor of the urinary tract. Of additional interest may be the fact that this was a lesion involving the left kidney. Mackey noted a considerably greater incidence of left kidney involvement over the right and theorized that this finding was possibly due to the left renal vein being more subject to obstruction because of its longer course and its crossing in front of the aorta. The compilation by Lazarus and Marks reveals only a slightly greater incidence of left kidney to right, 54.2 to 45.8 per cent, and McCrea's series reports the lesion as often in the right kidney as in the left.

SUMMARY

A huge cavernous hemangioma of the left kidney found at autopsy is reported.

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TYPE AND DISTRIBUTION OF CHOLINE ESTERASES OF URINARY COLLECTING SYSTEM OF DOG. THEIR RELATIONSHIP TO URETERAL PERISTALSIS AND POSSIBLE ROLE IN CONGENITAL ANOMALIES

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The mechanism by which the urine is transported from the renal parenchyma to the exterior has long been a problem to the urologist and attempts to correlate our knowledge of the anatomo-physiology of the collecting systems with the observed disorders of function noted clinically have not been very satisfactory.

The question as to whether the collecting systems are centrally innervated or completely autonomous in their action has been the subject of controversy during the past half century The well documented paper by Lapides, et al [1] provides an excellent summation of evidence for and against the various theories To this investigator Lapides provided good evidence in support of his contention that the ureter is a completely autonomous organ, but his further conclusion that its activity is but the expression of the known physiological phenomenon of the "stretch reflex" and that ureteral activity bears a direct relation to urine volume alone is difficult to explain in the light of his own observations on the variations in the rhythm and the character of the peristaltic wave

It seems cogent therefore to consider the possibility of an additional factor, a factor which would qualitatively influence the ureteral musculature and determine the efficiency of its activity and the disorder of which could account for the observed dysfunctions noted clinically In an attempt to define this factor it was determined to study the cholinesterases of the urinary collecting system

The following investigations were made

1. The distribution and the type of cholinesterase activity
2 The effect produced upon the cholinesterase activity of the ureteral musculature by the passage of a known cholinesterase inhibitor, diisopropylfluorophosphate (DFP) down the intact lumen of the ureter
3 The effect produced upon the ureteral peristaltic activity by the inhibition of the muscle cholinesterase activity
4 The isolation from the urine of the normal dog of a substance capable of inhibiting the cholinesterase activity of the ureteral musculature when passed through the lumen of the intact ureter

For the sake of clarity it is necessary to define initially certain terms, and we will adhere throughout the remainder of this text to the nomenclature used by Augustinsson,[2] viz

1 Acetylcholine esterase—with a higher affinity for its physiological substrate, acetylcholine, than any other known esterase

Note by editor Dr de Klerk's paper was awarded a prize in the annual Prize Essay Contest for 1952 sponsored by the American Urological Association

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[1] Lapides, J Physiology of intact human ureter J Urol , 59 501–537, 1948

[2] Sumner, J B and Myrback, K The Enzymes New York Academic Press Inc , 1950 (Part 1 of vol 1)

2. Cholinesterase—splits choline esters at a higher rate than noncholine esters, differing from the acetylcholine esterase in its activity-substrate relationship. Its physiological substrate is unknown.

I. THE DISTRIBUTION AND CHARACTER OF CHOLINESTERASE ACTIVITY IN THE CANINE URINARY COLLECTING SYSTEM

Method. The original intent was to determine this according to the method of Ammon as outlined by Augustinsson,[3] using the tissue homogenate as the source of the enzyme. We however were unable to homogenize the tissue and it was not possible to obtain a satisfactory quantitative estimation of the amount of enzyme-containing tissue present in the homogenate.

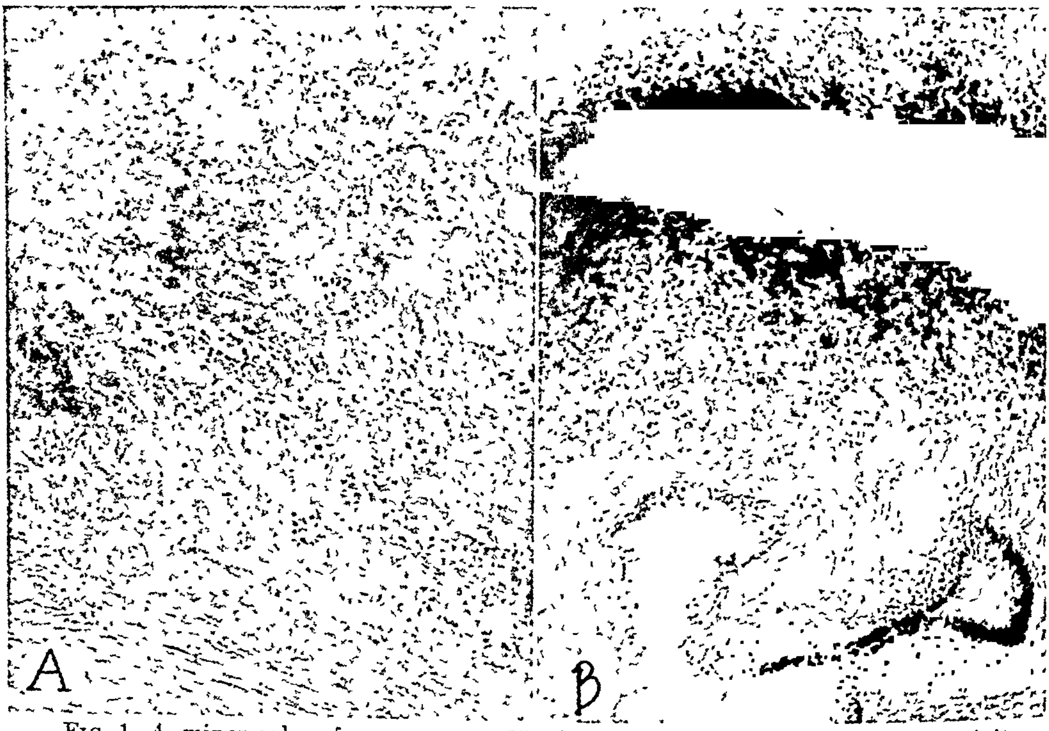

FIG. 1 *A*, minor calyx, frozen section, 25 microns, stained for cholinesterase activity, counterstained with eosin Marked evidence of cholinesterase activity consisting of deposition of brown-black CuS in tubules abutting on calyceal lumen. When stained for acetylcholine esterase *no* evidence of activity was found. (× 100) *B*, major calyx, frozen section, 15 microns, stained for cholinesterase activity, counterstained with aqueous phloxine. Note evidence of cholinesterase activity in circular muscle layer. Minimal activity noted in submucosa adjacent to muscle (× 100) When stained for acetylcholine esterase no evidence of activity could be determined.

Therefore the histochemical method of determination as outlined by Koelle, Koelle and Friedenwald[4, 5] was used. The tissues were removed from the intact

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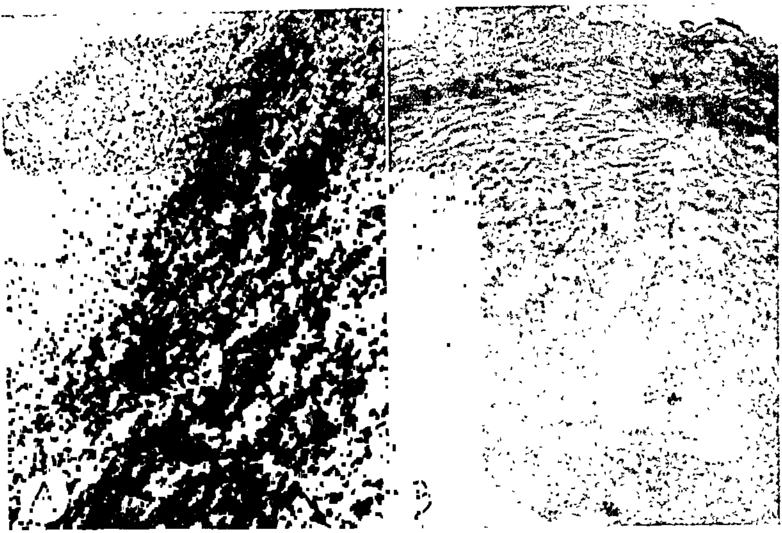


FIG. 2. *A*, renal pelvis (as in fig. 1, *B*). Note cholinesterase activity primarily in circular muscle fibers, slight evidence of activity in submucosa. As in previous section, no evidence [illegible] lureter, 15 microns, stained for [illegible] e. Note preponderance of cho- [illegible] activity in longitudinal fibers, and minimal evidence of activity in submucosa.

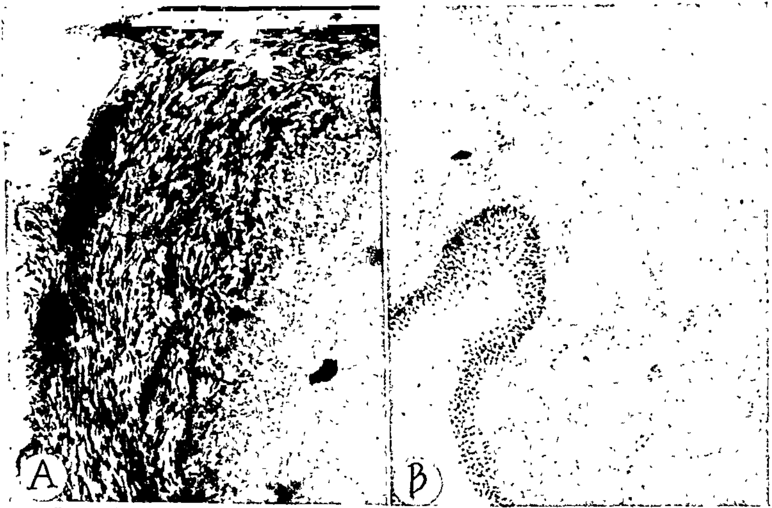


FIG. 3. *A*, midureter, 20 microns, stained for cholinesterase activity; counterstaining with phloxine in deep in this case but evidence of cholinesterase activity is visible in circular muscle fibers. *B*, midureter (as in *A*). Stained for acetylcholine esterase activity, counterstained with phloxine. Note absence of activity. This finding was uniformly encountered in all our sections of upper urinary tract, down to and including trigone.

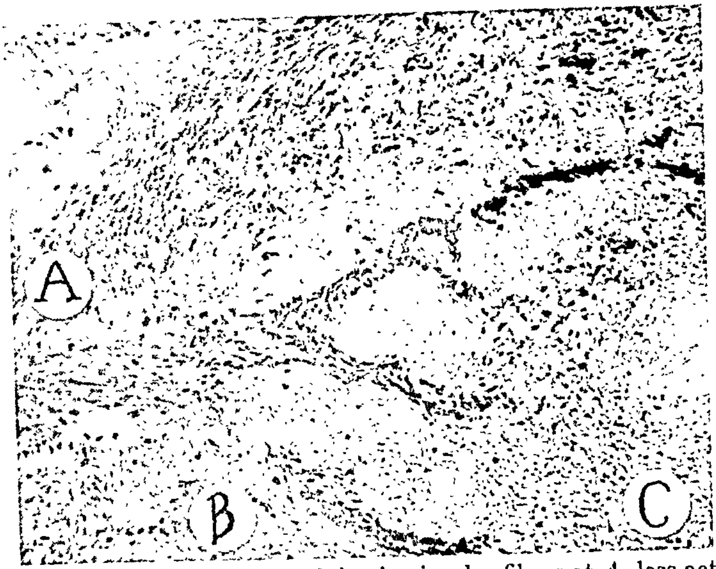


FIG. 4. Midureter (as in fig. 3, *A*). Activity in circular fibers at *A*, less activity in longitudinal fibers, *B*, and slight activity in submucosa, *C*.

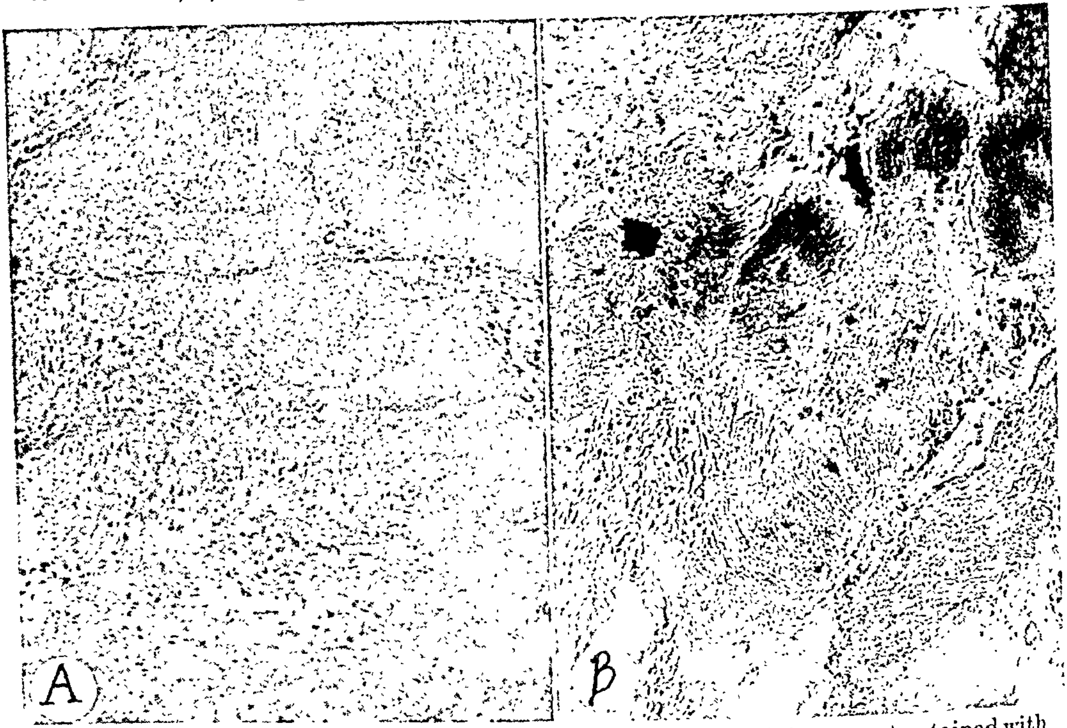
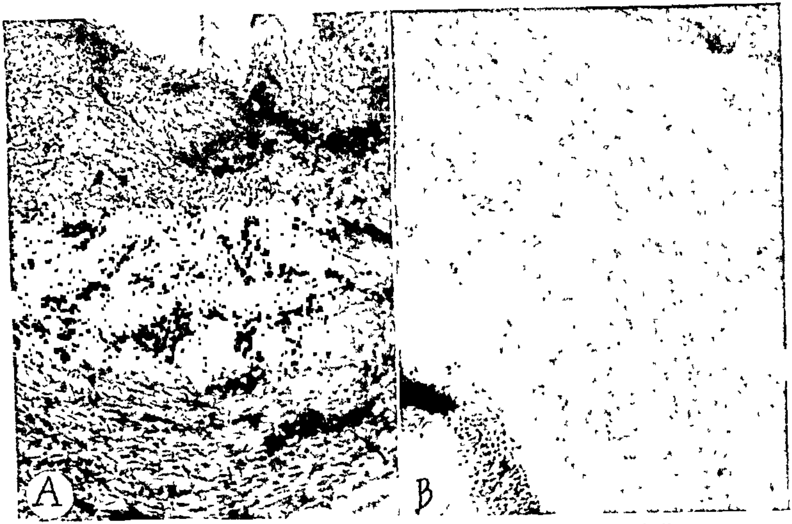


FIG. 5. *A*, trigone, frozen section, 15 microns, cholinesterase activity, counterstained with phloxine. Note evidence of activity in both muscle and interfascicular tissues. *B*, trigone (as in *A*). Stained for acetylcholine esterase activity. Note complete absence of any evidence of acetylcholine esterase activity. Dark areas represent deep red stain of phloxine.

animal by operation and immediately transferred into chilled saline, then stored at O° C. until required for study. Frozen sections were cut at a thickness varying from 15 to 30 microns and stained for cholinesterase activity (fig. 1).

By this method it was possible to determine the site and the type of cholinesterase activity in the tissue although no quantitative study could be performed.



F acetylcholine esterase acti muscle and interfascicular tissues. B, fundus of bladder (as in A). Stained for cholinesterase activity. Note absence of cholinesterase activity in the bladder proper.

Results. These indicated that the canine urinary collecting system, down to and including the vesical neck and trigone, showed a predominant cholinesterase activity. Little evidence of acetylcholine esterase activity could be found. The bladder showed primarily acetylcholine esterase activity. Cholinesterase activity was negligible (figs. 2–6).

In the ureter the major site of the activity was located in the circular muscle fibers and interfascicular tissues, with less cholinesterase activity in the longitudinal fibers, and slight but definite activity in the submucosa.

II. INHIBITION OF THE TISSUE CHOLINESTERASE OF THE DOG URETER BY THE PASSAGE OF A KNOWN INHIBITOR DOWN THE LUMEN OF THE URETER IN THE LIVING ANESTHETIZED ANIMAL

Method. McCombie and Saunders[6] have recorded that DFP irreversibly inhibits the activity of the cholinesterases. DFP is also known to have the further faculty of being rapidly absorbed when directly applied to cutaneous or mucosal surfaces. Koelle, Koelle *and Friedenwald report that DFP 10-6M solution will* irreversibly inhibit cholinesterase *in vitro.* DFP was utilized in the following experiment:

Six dogs were subjected to the same procedure at different dates. Under pentothal anesthesia bilateral paravertebral approaches were made and the ureters exposed at the lower pole of the kidney with as little disturbance of the tissues as

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[6] McCombie, H. and Saunders, B. C.: Alkyl fluorophosphonates; preparation and physiological properties. Nature (London), 157: 257–289, 1946.

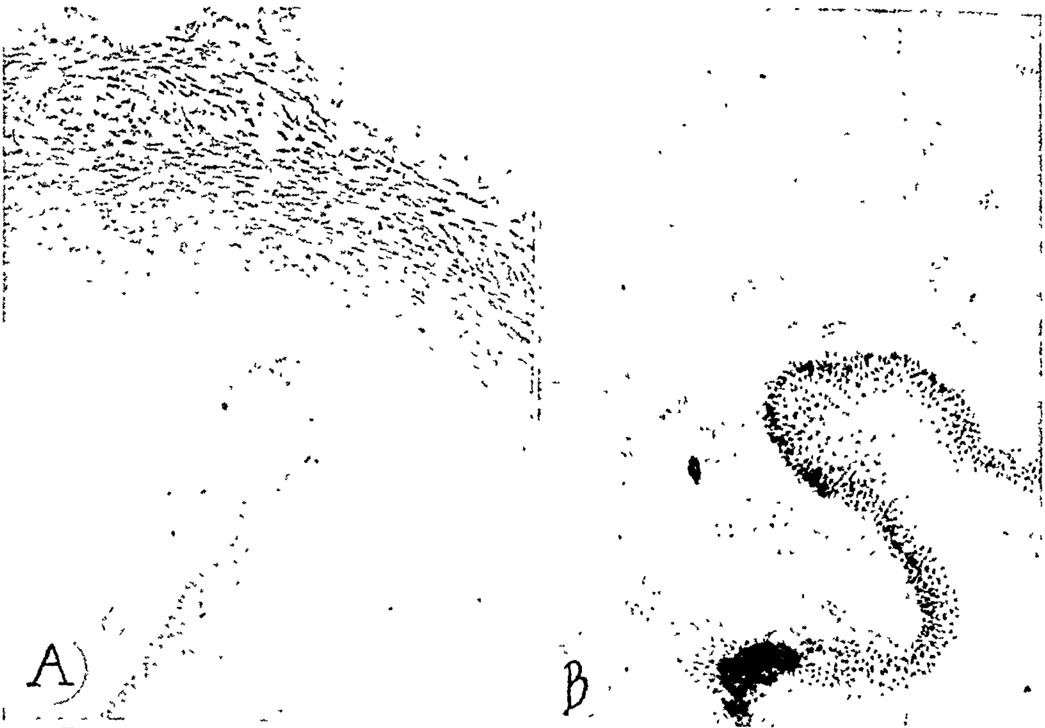

FIG. 7. *A*, irrigation of ureteral lumen with saline, showing presence of cholinesterase activity after perfusion of right ureter for 1 hour with normal physiological saline at room temperature. Counterstained with phloxine. *B*, irrigation of ureter with DFP 10-6M solution. Left ureter of same animal as in *A*, after 1 hour irrigation, showing complete inhibition of cholinesterase activity. Lightly counterstained with phloxine.

possible. Identical procedures were then carried out on both sides: Ureterotomies were done on the contravascular aspect of the ureters and intubated with a polyethylene tube. A silk ligature was applied to prevent slipping or backflow. The wounds were closed and the animal turned on its back. Through a muscle-splitting approach the ureters were isolated at the ureterovesical junction and similar ureterotomies carried out, the ureters again catheterized by polyethylene tubes and held in place by a ligature. The wounds were closed. In effect, the ureters were isolated and cannulated on both sides with a minimum of disturbance of the normal relations. Both ureters were irrigated with 20 drops of normal saline per minute at room temperature. After 15 minutes the experimental side was replaced by DFP 10-6M solution in normal saline. The control side retained the normal saline drip. After one hour the DFP was removed from the experimental side and replaced again by normal saline and allowed to continue for 15 minutes. The dog was immediately opened and while still alive both ureters were removed rapidly and placed in cold saline, thence stored at 0° C. until they could be sectioned and stained.

Results. In all six experiments identical results were obtained (fig. 7). The tissue cholinesterase activity on the control side showed no alteration; the cholinesterase activity on the experimental side was completely inhibited and the cholinesterase activity in that portion of the experimental side which was proximal to the site of in flow and therefore not influenced by the DFP, showed no loss of activity.

III. WILL INTERFERENCE WITH THE BLOOD SUPPLY AT THE SITE OF THE URETEROTOMIES IN THE PREVIOUS EXPERIMENT AFFECT THE TISSUE CHOLINESTERASE ACTIVITY?

Method. A left nephrectomy was carried out, the stump of the ureter being ligated with silk. The juxtavesical portion of the ureter was transected and ligated. The right ureter was left alone to serve as a control. After three weeks the ureters were removed under the identical conditions as in the previous experiment and stained.

Results. There was no apparent diminution in the cholinesterase activity on either side (fig. 8).

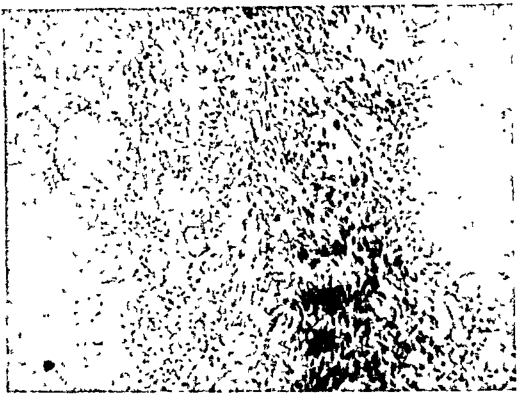

Fig. 8. Midureter, frozen section. Cholinesterase activity 3 weeks after nephrectomy and transection and ligation of the juxtavesical portion of ureter. Lightly counterstained with phloxine. Note persistence of activity.

IV. WILL THE INHIBITION OF THE TISSUE CHOLINESTERASE, AS CARRIED OUT IN II, AFFECT URETERAL PERISTALSIS?

Method. A procedure identical to experiment II was done on 6 dogs. The lower ureterotomy tube, however, was connected to a Phipps and Byrd double membrane liquid manometer from which recordings were made upon a Phipps and Byrd Kymograph drum.

Results. Within ten minutes after commencing the DFP infusion it was observed that the peristaltic rhythm was becoming irregular, the height of the waves becoming smaller. At the end of 12 minutes all peristaltic activity had ceased. In subsequent experiments the rate at which this cessation of peristalsis occurred was directly proportional to the speed of the infusion. On the control side the peristalsis persisted throughout the duration of the experiment (fig. 9).

V. IS THE URINE OF THE DOG ABLE TO EXERT AN EFFECT UPON THE TISSUE CHOLINESTERASE OF THE URETER?

If, from the foregoing experiments, it could be presumed that the cholinesterase activity of the ureteral musculature could be influenced by the contents of

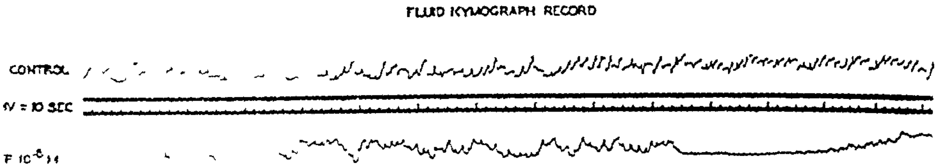

FIG. 9. Fluid kymograph recording of effect produced by passage of DFP 10-6M solution down lumen of ureter in living anesthetized animal. Upper recording shows graph obtained on control ureter, lower shows effect on ureteral peristalsis after commencement of DFP perfusion at *A*, cessation of peristalsis, *B*; and rise in intraluminar pressure *C*.

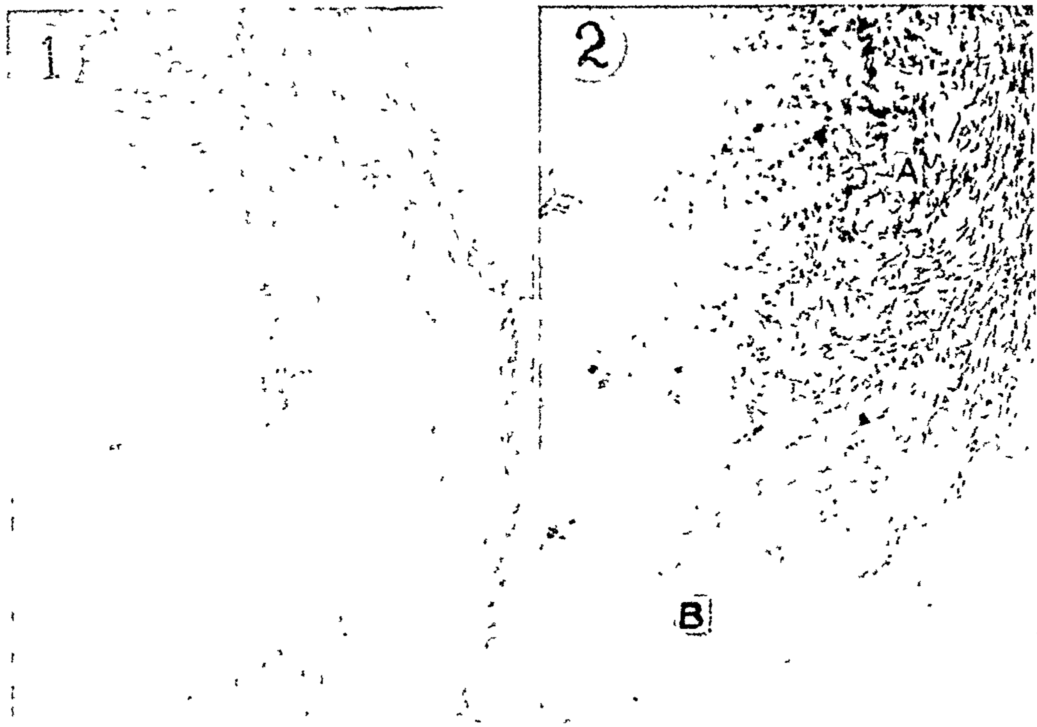

FIG. [illegible] A, right control ureter, [illegible] section, 15 microns, persistence of cholinesterase activity after initial perfusion for 1 hour with physiological saline at room temperature. *B*, left ureter, frozen section, 15 microns, showing patchy inhibition produced after perfusion of ureter with extract of [illegible] in experiment V. Still definite evidence of cholinesterase activity at *A* and almost complete absence of activity at *B*.

Sections taken at various other areas in same ureter showed no uniformity in site or amount of cholinesterase inhibition in any section.

the ureteral lumen and that this would exert an effect on the character of the ureteral peristaltic wave, it seemed reasonable to seek such a modifying agent in the urine itself

In 1908 Abelous and Bardier[7] found a pressor base in the urine which they named "urohypertensin." Bain[8] in 1914 concluded that this was iso-amylamine. In 1942 von Euler and Sjostrand[9] found large amounts of a pressor principle in the urine of normal subjects In 1944 von Euler[10] had isolated this substance as a crystalline picrate which, pharmacologically was not unlike acetylcholine but more akin to nicotine We decided to study the effect of this substance on the activity of the ureteral cholinesterase

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[7] Abelous, J. E. and Bardier, E. Action Hypertensive de l'Urine de l'Homme Normal. J Physiol. Path. Gen., 10: 627-633, 1908.

[8] Bain, W.: The pressor bases of normal urine. Quart. J. Exp. Physiol., 8: 229-242, 1915

[9] van Euler, U. S and Sjostrand, T.: Pressor substances in urine and plasma from normal and hypertensive subjects Nature (London), 151: 168-169, 1943.

Method We followed von Euler's method in all essentials, viz, concentrating 10 liters of dog urine down to 1 liter in vacuo, subjecting the concentrate to continuous ether extraction, removing the active substance from the ether with acidified water, steam distilling this extract at pH 10 No attempt was made to obtain crystals by fractionated crystallization as was done by von Euler The extract was again evaporated under vacuum in a water bath to remove any trace of ether which still persisted

The resultant extract was then diluted 1:1000 in normal saline

The procedure as outlined in experiment II was then carried out with the single exception that to date this has only been done on three animals in view of the lengthy procedure required to obtain the extract

Results There was a patchy inhibition of esterase activity in the ureteral muscle (fig 10) This was also noted in numerous other sections taken at various points along the course of the ureter in the three animals done In some areas there was complete inhibition, in others partial There was no uniformity of site or degree of inhibition The feeling was that this observation could be explained on the basis of a rapidly reversible inhibition of the esterase by the inhibitor in the urine What the characteristics of this inhibitor are we do not know at this point

DISCUSSION

Until recently the majority of workers have indicted the acetylcholine esterase as the only esterase involved in synaptic transmission However, Mendal, et al,[11] Heymans, et al,[12] and Koelle[4] have produced evidence that leaves no doubt that the cholinesterases also play an important role in this process Koelle mentions the work of Comroe and later Grob who demonstrated that parenterally administered doses of DFP which are too small to modify neuromuscular transmission significantly had a marked effect on gastro intestinal motility These observations appear to be further strengthened by the noted absence of acetylcholine esterase in the pelvi ureteral musculature of the dog (fig 3, *B*)

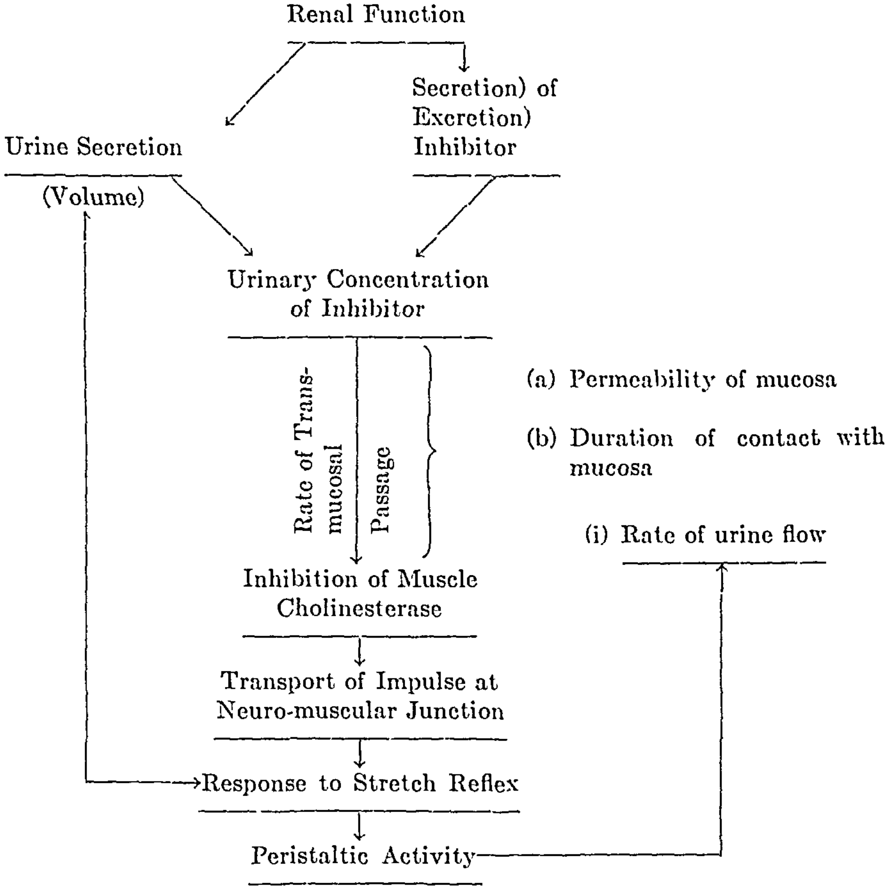
If we accept the postulate that the character of the ureteral peristalsis is not alone dependent upon the known factors of urine volume and stretch reflex, and that there must be an additional factor influencing this activity, it appears that this factor may be a constituent of the urine which acts directly upon the tissue cholinesterase of the ureteral musculature It has been observed that the greater preponderance of the cholinesterase activity of the ureter is located in the circular muscle fibers, with less evidence of activity in the longitudinal fibers, although there are areas where the activity extends into the submucosa (figs 3, *B* and 5,

[10] von Euler, U S Acta Physiol Scandinav, 7 285–287, 1944

[11] Mendal, B, Hawkins, R D and Nishikawara, M Cholinesterase levels in plasma and tissues Am J Physiol 154 495–498, 1948

[12] Heymans, C Verbeke R and Votava Z Cholinesterases Symptômes Cholinergiques et Sensibilité à l'Acetylcholine Arch Int de Pharm et Ther, 77 486–494, 1948

B). The alteration in ureteral peristalsis following inhibition of the cholinesterase by a known inhibitor, such as DFP, which is apparently able to exert its effect by direct passage through the intact mucosa of the ureter was noted (fig. 10, *B*). The evidence that canine urine appears to contain a cholinesterase inhibitor under laboratory conditions suggests the following schema of the factors associated with ureteral peristalsis:


Renal Function
Secretion) of
Excretion)
Inhibitor
Urine Secretion
(Volume)
Urinary Concentration of Inhibitor
Rate of Trans-mucosal
Passage
(a) Permeability of mucosa
(b) Duration of contact with mucosa
(i) Rate of urine flow
Inhibition of Muscle Cholinesterase
Transport of Impulse at Neuro-muscular Junction
Response to Stretch Reflex
Peristaltic Activity

It will be appreciated that ureteral peristalsis will be influenced both by the amount of inhibitor at the site of cholinesterase activity and the urine volume. Variations in the concentration of the inhibitor will produce variations in the peristaltic pattern. *Conversely absence of the inhibitor does not preclude peristaltic activity*. Finally, if the flow of urine is prevented, there will be an increased concentration of inhibitor at the neuromuscular junction, and a state of persistent spasm of the ureteral musculature will be maintained.

Consideration of the role of the cholinesterases in the pathogenesis of so-called congenital strictures of the ureter must pre-suppose the existence of a fetal urinary excretion to be able to account for the existence of these lesions at birth. That the fetal kidneys do excrete urine in the lower animals has been established.[13] Kjelberg and Rudhe[14] demonstrated the presence of fetal urinary excretion in the human at the fourth–fifth month of pregnancy In these conditions the development of these anomalies may well occur as follows·

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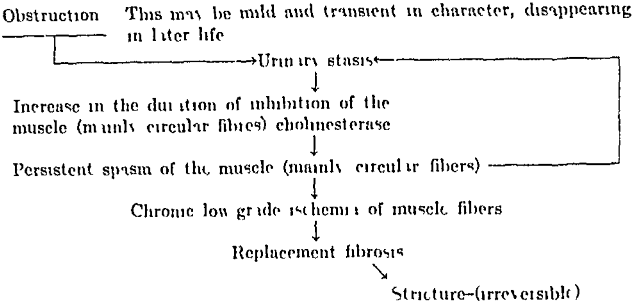
[13] Smith, H.: The Kidney. New York: Oxford Medical Publications, 1951.

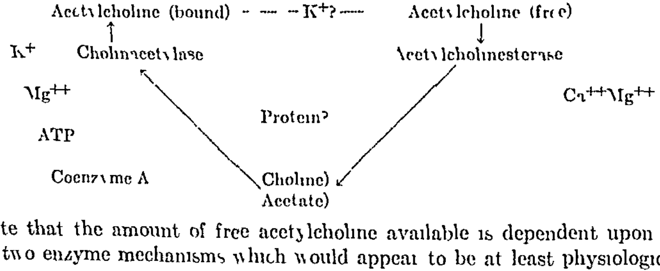
[14] Kjelberg, S. R. and Rudhe, U.: The fetal renal secretion and its significance in congenital deformities of the ureters and urethra. Acta Radiologica, **31:** 243–249, 1949.


Obstruction
This may be mild and transient in character, disappearing in later life
Urinary stasis
Increase in the duration of inhibition of the muscle (mainly circular fibres) cholinesterase
Persistent spasm of the muscle (mainly circular fibers)
Chronic low grade ischemia of muscle fibers
Replacement fibrosis
Stricture–(irreversible)

The trigone and internal vesical orifice have the same enzyme characteristics as the muscle fibers of the ureter (fig 6, *B* and 7, *A*) It is therefore apparent that the same factors mentioned above may apply here

However, if we consider the pathogenesis of megalo-ureter (Caulk[15]) which has recently been defined by Meredith Campbell[16] as a unilateral or bilateral wide dilatation of the ureter and pelvis in the absence of intravesical obstruction, the problem becomes more complex It is necessary at this stage to digress somewhat and consider in greater detail the various processes involved in the metabolism of acetylcholine

According to Augustinsson[2] the present-day concept of the metabolism of acetylcholine can be diagrammatically represented as follows



Note that the amount of free acetylcholine available is dependent upon at least two enzyme mechanisms which would appear to be at least physiological antagonists

Torda and Wolf[17] state that in the rat the ability to synthesize acetylcholine is dependent upon the presence of an intact hypophysis, which apparently exerts its effect through the medium of ACTH Among the many factors considered by them to be capable of influencing this process are the following substances estrogens, pregnenalone, epinephrine, thymus, thyroid and pancreatic extracts, and certain other steroids

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[15] Caulk J [illegible] ol , 9 315 330 1923
[16] Campbe [illegible] Urology Philadelphia W B Saunders Co 1951
[17] Torda, C [illegible] Acetylcholine synthesis Science, 103 645–646, 1946

Hydro-ureter of pregnancy is a well known clinical entity. Chronic ureteral obstruction by the fetal head with superimposed infection producing permanent changes in the more advanced cases is considered by many as the cause of this condition. This concept has, however, been seriously questioned as far back as 1928 by J. Hofbauer[18] who postulated the theory that the atony of the ureteral musculature may be upon the basis of intoxication by the increased circulating bile acids known to be present in the pregnant female. Later, van Wagenen and Jenkins[19] demonstrated in monkeys that the dilatation will persist and even increase following hysterotomy if the uterus is closed with the placenta intact. If these changes are on the basis of a disturbance of acetylcholine synthesis due to an altered hormonal picture, it is apparent that its effect upon the mother is usually not marked as we seldom see these gross hydro-ureters in pregnant women. However, in the fetus we have the additional factors of an enlarged thymus, which Torda and Wolf implicate as an inhibitor of acetylcholine synthesis, and the insertion, in tandem as it were, between the circulation of the mother and the fetus, of the placenta which von Wagenen and Jenkins' work seems to implicate in this process.

Therefore the pathogenesis of megalo-ureter may well be on the basis of decreased synthesis of acetylcholine with resultant loss of muscular tone and hydrodynamic distention of the flaccid ureter by the fetal urinary secretion. This decrease in acetylcholine synthesis possibly is produced through the mediation of the thymus and placenta.

SUMMARY

A study of the tissue cholinesterase activity of the urinary collecting system of the dog is presented.

It is established that the pelvi-ureteral musculature of the dog contains a cholinesterase alone. There is no evidence of acetylcholine esterase activity in these tissues. This observation is also established with regard to the trigone of the bladder.

The remainder of the bladder musculature exhibits a predominant acetylcholine esterase activity and minimal evidence of cholinesterase activity.

The cholinesterase of the dog ureter can be inhibited *in vivo* by the passage of DFP 10-6M solution through the lumen.

Inhibition of the cholinesterase of the dog ureter results in cessation of ureteral peristalsis and increased ureteral tone.

Evidence is presented which suggests the existence of a cholinesterase inhibitor in the urine of the normal dog.

The implications of these findings and their possible role in the normal ureteral peristalsis are discussed.

The possible role of the acetylcholine metabolic cycle in the pathogenesis of the congenital abnormalities of function of the urinary collecting system is discussed.

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[18] Hofbauer, J.: Structure and function of the ureter during pregnancy. J. Urol., *20:* 413–426, 1928.

[19] van Wagenen, G. and Jenkins, R. H.: An experimental examination of factors causing ureteral dilatation in pregnancy. J. Urol., **42:** 1010–1020, 1939.

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TRIPLICATE URETER

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Some type of duplication of the ureter is said to occur in 0.5 per cent of routine autopsies.[1] The occurrence of congenital ureteral anomalies of number of a higher degree is extremely rare. A search of the literature reveals only thirteen recorded cases of triplication of the ureter.[2-9]

Triplicate ureter exists in the following variations:

a) *Complete ureteral triplication* with three ureteral orifices. This has been reported four times. In each instance it has been on the right side.

b) *Double ureter with one bifid.* In this type there are two ureteral orifices with one of the ureters dividing above the bladder level. This has been reported twice.

c) *Trifid ureter.* One finds here a single ureteral orifice with the ureter dividing into three component parts above the bladder level. This has been recorded seven times with a different pattern in each case.

Embryologically, the ureteric bud appears at about thirty days as an outgrowth from the dorsal surface of the mesonephric duct where the latter bends ventrally to enter the cloaca. A double or triple ureter is caused by the development of more than one ureteric bud from the mesonephric duct or by clefting of a single ureteral bud.

The following case is an additional example of double ureter with one bifid demonstrated by retrograde pyelography.

CASE REPORT

A 31 year old Negro was seen in January 1953 because of burning on urination and mild frequency, urgency and nocturia of 1 week's duration. There was no history of back pain, chills, fever or hematuria. He admitted no previous genito urinary difficulties, except gonorrhea 11 years previously, and there was no known kidney disease in the family.

The abdomen was flat. No costovertebral angle or abdominal tenderness was present. The left kidney was not palpable. The lower pole of the right kidney was palpable and moved on respiration. No other abdominal masses were felt. The external genitalia were completely normal. There was no urethral discharge. Rectal examination revealed a normal sized prostate with scattered areas of induration suggestive of chronic prostatitis. The blood pressure was 124/76,

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Read at the annual meeting of the Mid Atlantic Section of the American Urological Association in Washington, D. C., April 23, 1954.

[1] Campbell, M. F.: Pediatric Urology. New York: Macmillan, 1937, vol. 1.

[2] Burt, J. C., Lane, C. M. and Hamilton, J. L.: J. Urol., 46: 235, 1941.

[3] Lau, F. T. and Henline, R. B.: J. A. M. A., 96: 587, 1931.

[4] Miller, J.: Brit. J. Urol., 10: 249, 1938.

[5] Woodruff, S. R.: J. Urol., 46: 376, 1941.

[6] Smith, I.: Brit. J. Surg., 34: 182, 1946.

[7] MacLean, J. T. and Harding, L. W.: J. Urol., 54: 381, 1945.

[8] Withycombe, J. F. R.: Brit. J. Surg., 38: 113, 1950.

[9] Gill, R. D.: J. Urol., 68: 140, 1952.

temperature, 98.6F. Urinalysis: Specific gravity, 1.020; pH, 7.0; albumin, trace; glucose, negative. Sediment: Clumps of white blood cells; occasional red blood cell; no casts; numerous Gram negative bacilli.

Excretory urography revealed prompt appearance of the contrast medium bilaterally. The left upper urinary tract was well outlined and appeared completely normal. The right upper urinary tract was incompletely outlined but suggested the presence of a triple pelvis.

A diagnosis of bacillary cystitis was made, probably secondary to chronic prostatitis. In addition, a congenital anomaly of the right kidney was suspected.

The patient was placed on 3 gm. gantrisin daily for one week. The symptoms subsided promptly and at the end of this time there were 3–5 white blood cells per high powered field in the sediment of the centrifuged urine. The patient remained asymptomatic and 2 weeks later cystoscopy was performed.

A 16F Brown Buerger cystoscope was introduced to the bladder. The prostatic urethra was congested. There was no significant prostatic enlargement. There were no tumors, ulcers, calculi or trabeculation. The apex of the trigone was injected. The left ureteral orifice was normally located and ejected clear urine. At the right angle of the trigone were seen two normally appearing ureteral orifices in tandem. Both ejected clear urine. A third orifice could not be found on the right. Indigo carmine appeared in 4 minutes after intravenous injection from the left ureteral orifice and in 5 minutes from both orifices on the right. The intensity of color was marked from all three orifices.

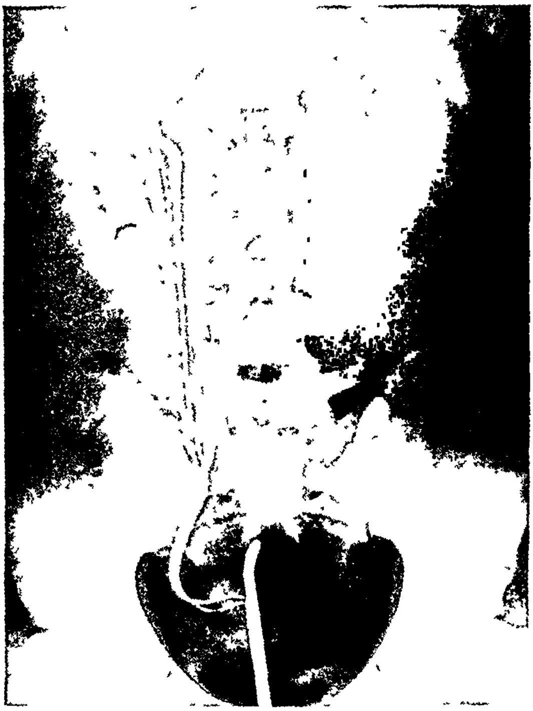

Fig. 1. Right retrograde pyelogram demonstrating three pelves and a double ureter with one bifid.

A 5F ureteral catheter was introduced into the lower right ureteral orifice and passed 28 cm. without encountering obstruction. A 5F ureteral catheter was introduced into the upper right ureteral orifice and passed 6 cm. where a hang was encountered and the catheter was left at this level. Urine collected from both catheters was negative on microscopic examination. The patient was placed in slight Trendelenburg position and a retrograde pyelo-ureterogram made by injecting both catheters with 20 per cent skiodan (fig. 1) revealed a double right ureter with one bifid. A ten minute delayed upright film demonstrated that all three pelvic segments and ureters drained completely.

DISCUSSION

As is usual in duplication, the upper pelvic segment and ureter in this case drained through the lower ureteral orifice. The ureter from the upper ureteral orifice divided in the region of the midportion of the sacro-iliac synchondrosis and the two resulting ureteral segments crossed just below the transverse process of the fourth lumbar vertebra and coursed upward to supply the middle and the lower segments of the triple pelvis.

The clinical and embryological significance of triple ureter would not appear to be different from double ureter. The increased risk of infection and obstruction with subsequent complications would seem to be present, although in this case drainage was adequate.

SUMMARY

A case of triple ureter demonstrated by retrograde pyelography is added to thirteen previously reported cases. Only two of the previous cases represent this type of the variation.

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ECTOPIC URETERAL REMNANT PERSISTING AS CYSTIC DIVERTICULUM OF THE EJACULATORY DUCT: CASE REPORT

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The anomaly of the ectopic ureter entering the seminal tract is rather loosely stated by several standard text books of Urology to be not uncommon. A review of the American literature reveals that since 1852 a total of only 41 cases have been reported. Of this group, 32 were discovered at autopsy examination and nine were diagnosed clinically. These latter cases were reported by Day, 1924; Culver, 1937; Hamer et al., 1937; Minuzzi and Torressi, 1940; Riba et al., 1946; Engel, 1948; Hamilton and Peyton, 1950; Meisel, 1952; and Pasquier and Womack, 1953. Our case represents the tenth instance of this anomaly in which an accurate diagnosis was made before operation and corrective treatment was successfully completed.

The condition may be associated with a functioning kidney, either solitary or double. In such instances the ureter connects either with the urinary tract or, sometimes in the female, the genital tract. Usually the renal remnant is infected and the presenting symptom in these cases is persistent pyuria and quite often terminal hematuria. A rare exception to this generalization was the case reported by Engel in which the urine was clean. In the majority of patients the kidney is rudimentary or aplastic. In such cases the continuity between the renal remnant and ureter may be absent, secondary to congenital stricture or failure of anastomosis between the ureteral bud and the metanephros. On the other hand, although it may be atrophic and fibrosed, the ectopic ureteral segment often persists as a demonstrable tube ascending cephalad toward the region of the lumbar fossa or may, in certain cases, assume a cystic or globular shape close to the site of origin.

The embryologic origin of ureteral ectopy can be summarized as follows:

In the four to five mm. embryo the ureteral bud arises from the mesonephric duct (wolffian duct) near its caudal junction with the pars vesico-urethra and grows in a dorsal and cranial position to the parent duct. By a process of absorption in the 11th to 14th mm. stage of development the ureter moves free of the mesonephric duct into a lateral and cranial position that corresponds to its final trigonal location. The mesonephric duct remains situated in the midline and continues to grow caudally and finally gives origin to the vas deferens, ampulla of the vas and the ejaculatory ducts and contributes to the prostatic urethra. The seminal vesicle arises as a lateral evagination from the ampulla of the vas at the 60 mm. stage of embryonic development.

This process of differentiation is well demonstrated in the schematic presentation taken from Arey (fig. 1). The most commonly accepted theory of

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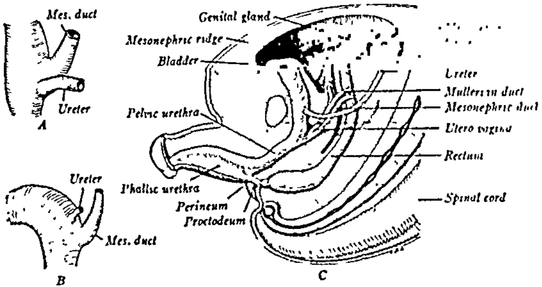

FIG. 1. Completed division of human cloaca, and associated changes, shown by models viewed from left side, *A*, *B*, at 6 weeks and 7 weeks, respectively, illustrating absorption of left ureter and mesonephric duct into wall of bladder. *C*, at 9 weeks (after Keibel). From Arey: Developmental Anatomy, 5th ed. Philadelphia: W. B. Saunders Co., 1941.

anomalous development proposes that if the early junction between the mesonephric duct and the ureteral bud fails to dissolve, the ureteral opening is carried caudally and medially and may empty into the posterior urethra, vas deferens, ampulla of the vas, ejaculatory duct or seminal vesicle. An alternate theory presumes the complete absorption of the distal mesonephric duct leaving the ureter lateral and caudal to the vesicomesonephric connection. Eventually the mesonephric duct moves caudally and during this shift from cephalad to caudad positions different varieties of fusion between the ureter and mesonephric duct may occur.

Since the preoperative studies in our case were also suggestive of a cystic diverticulum arising from the region of the seminal vesicle, a brief résumé will be made at this point of cyst of the seminal vesicle. There have been 9 cases of seminal vesicle cyst recorded in the American and English literature since Smith's original report in 1872. However, due to absence of positive radiographic and histologic findings in several of these cases, it is possible that a few of them may have actually been cysts arising from an ectopic ureteral bud or supernumerary vas deferens. In two of the clinically reported cases of ectopic ureter connecting with the seminal vesicle, the associated condition of seminal vesicle cyst due to stricture of the ejaculatory duct was observed.

Englisch has classified cysts of the seminal vesicle according to origin and anatomic position as follows:

1) Cyst of the wolffian body or duct, situated laterally in the neighborhood of the vas deferens and posterior wall of the bladder.

2) Cyst of the müllerian duct, situated in the region of the posterior wall of the bladder and close to the midline.

3) Cyst of the sinus pocularis, extending up beneath the floor of the bladder in the intervesicular region.

4) Cyst arising in the seminal vesicle from obstruction of the vesicular outlet.

Voelcher considers group 4 to represent the true cysts of the seminal vesicle. Although the exact origin of these retrovesical cysts may be extremely difficult to demonstrate clinically, it is felt that this rather rigid classification should be accepted and adhered to in making the diagnosis of seminal vesicle cyst. When this condition is present, either primarily or secondarily, the presenting symptoms are lower abdominal distress that is episodic in character, rectal burning and smarting with intermittent difficulty in defecation and, on occasion, postejaculatory distress. A cystic mass is usually discovered on rectal examination and spermatozoa are invariably present within the cystic contents.

CASE REPORT

A 32 year old white man was admitted to the Cleveland Veterans Administration Hospital on March 18, 1952 complaining of recurrent, moderately severe, left inguinal and perineal discomfort and severe ejaculatory and postejaculatory distress. He denied any urinary symptoms, and dated the onset of his difficulties to September 1945, when he experienced the onset of uncomplicated diarrhea consisting of 3 to 4 liquid stools per day. This condition was controlled with the use of paregoric and sulfa medications but it continued to recur and the patient was hospitalized in an Army institution. A diagnosis was made of congestive seminal vesiculitis and congenital absence of the left kidney. The latter finding was substantiated by cystoscopy at which time absence of the left ureteral orifice was noted. The patient was treated with rectal heat and sulfa drugs with some relief. Following discharge from the service he remained asymptomatic except for occasional dull, aching discomfort in the left perineal region with occasional radiation to the left medial thigh. In September 1951, the patient had a recurrence of liquid bowel movements with sharp pain in the region of the glans penis. These symptoms continued to December 1951, at which time he began to have bowel movements of semiformed stools whenever he urinated. In January 1952, he was seen by an urologist and subjected to cystoscopy. He was informed that the left floor of his bladder was elevated by a cystic mass and more investigation was advisable.

The patient's blood pressure was 130/80. The positive physical findings consisted of the presence of a well-healed right McBurney abdominal scar and a slightly thickened and indurated left epididymis. The prostate, per rectum, was small, firm and nontender. The seminal vesicles were enlarged, with the left more prominently so.

The urine was microscopically clean. The hemogram was normal and the serology was negative. The chest film was within normal limits. A plain film of the abdomen revealed absence of the left renal shadow, and excretory urography showed a normally functioning right kidney with no evidence of function on the left side. In the left upper abdominal quadrant just lateral to the vertebral column, between the eleventh and twelfth posterior ribs, an area of circular calcification was present. Multiple projections taken of this focus placed it within the anatomical location of the left kidney. On March 25, 1952 cystoscopy was performed under spinal anesthesia. An apparently extrinsic mass was noted elevating the left floor of the bladder. No ureteral orifice was observed. The impression centered about the presence of a cyst of the seminal vesicle or an ectopic ureter ending blindly in the left seminal vesicle. On April 10, 1952 repeat

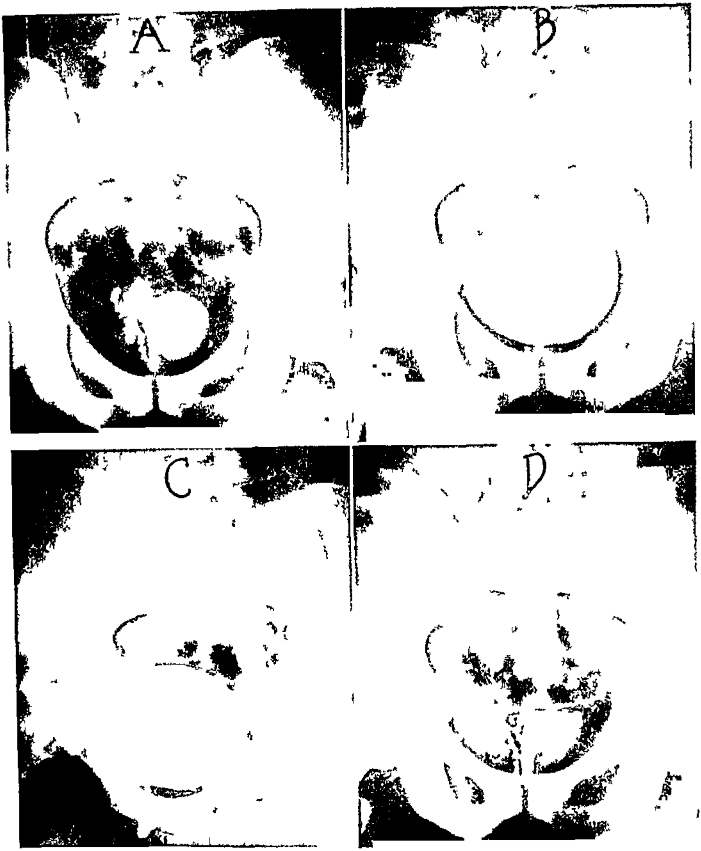

FIG 2 *A*, cyst injected transvesically demonstrating continuity with seminal tract *B*, retrograde cystogram demonstrating cyst as separate from bladder *C*, same as *B*, in right posterior oblique view *D*, connection of cyst with left ejaculatory duct as demonstrated by injection of left vas

cystoscopy was performed and a cystoscopic needle was inserted through the bladder floor into the subvesical mass and a large amount of turbid, brownish-gray fluid withdrawn that contained many immobile sperm Diadrast was then injected into the cystic space obtaining the picture demonstrated in figure 2, *A* This revealed a well-defined cystic space communicating with the seminal vesicle At the time of this procedure the patient complained of moderately severe pain in the left groin and perineal region similar to that previously experienced in the presenting complaint A retrograde cystogram was then obaccepted and adhered to in making the diagnosis of seminal vesicle cyst. When this condition is present, either primarily or secondarily, the presenting symptoms are lower abdominal distress that is episodic in character, rectal burning and smarting with intermittent difficulty in defecation and, on occasion, postejaculatory distress. A cystic mass is usually discovered on rectal examination and spermatozoa are invariably present within the cystic contents.

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SUMMARY

The case presented represents the anomaly of an ectopic ureteral segment connecting with the ejaculatory duct and persisting as a cystic diverticulum Urinary symptoms were absent as there was no apparent connection with the functional urinary tract The chief complaint was left perineal and groin pain with ejaculatory and postejaculatory distress Speculatively, the focal calcification in the upper left abdomen may represent an aplastic kidney, but this has not been confirmed. The patient obtained complete relief of symptoms following suprapubic removal of the cyst

We wish to thank W B Saunders Company for their permission to utilize an excerpt from Hinman's *Principles and Practice of Urology*, and for the reproduction of figure 1 from Arey's *Developmental Anatomy*.

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DIAGNOSIS OF VAGINAL ECTOPIC URETER BY VAGINOGRAM

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The proper surgical management of the patient suffering from urinary incontinence due to an ectopic ureteral orifice requires accurate localization of the source of the ectopic ureter. The usual site of an extravesical orifice in the female is the vestibule, near the urethral meatus, where it can be seen on careful inspection and catheterized partially or completely, so that a retrograde pyelo-ureterogram may be obtained which will give conclusive evidence of the origin of the ectopic ureter. Less commonly the anomalous ureter opens into the vagina, and in that location the diagnostic difficulties are greatly increased.

The excretory urogram may be of help since in most instances there is reduplication of the renal pelvis and ureter, the ectopic ureter almost always arising from the upper pelvis. However, there is often no excretion of the urographic medium by the involved segment of kidney either because of its rudimentary size, or due to advanced hydronephrosis or severe infection, and the pyelogram may show nothing suggestive of the anomaly. Direct visualization of the ectopic orifice in the vagina is very difficult, whether one uses a speculum or various types of cystoscope or endoscope; the intravenous administration of indigo carmine is rarely of any assistance because of the poor function of the involved portion of kidney. Even when the orifice is seen a catheter usually cannot be introduced into it at all or cannot be passed sufficiently to produce a ureterogram or pyelogram. One may therefore still be unable to determine which kidney is responsible for the urinary incontinence. In several instances of vaginal ectopic ureter reported in the literature, after all of the usual diagnostic measures described, it still could not be demonstrated which kidney possessed the ectopic ureter, so that surgical exploration of both kidneys was necessary to determine this vital point.

As a diagnostic aid in cases of ectopic vaginal ureter the authors propose the use of a vaginogram to demonstrate the ectopic ureter by reflux. Thorough search of the literature indicates that this procedure has not been employed heretofore. In the case reported herewith it proved to be of inestimable value, and was the only means of determining which kidney required surgical intervention.

CASE REPORT

A. F., a white girl of 7 years, was admitted to the Jewish Hospital on November 7, 1951 because of urinary incontinence which had been present since birth. The child voided satisfactorily through the urethra, without frequency or dysuria, but there was also constant dribbling of small amounts of urine from the region of the vulva, unaffected by her position or by the time of day. Excoriation of the vulva and thighs had been present since infancy. The patient had been consid-

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ered an enuretic with an associated "behavior problem" because she was very shy and sensitive. The usual therapy of various kinds for functional enuresis had been administered, but without improvement, and urological study was therefore requested.

The child had been born prematurely and at birth weighed 2 pounds, 13 ounces, but subsequent growth was satisfactory, although she was still small for her age. Aside from measles and chicken-pox her previous history was otherwise negative.

On examination neither kidney was palpable and there was no tenderness over either costovertebral angle. The bladder was not distended. There was marked redness about the vulva and inner aspects of both thighs. The urethral meatus was normal in location and appearance. A slight, but constant flow of clear urine occurred from the vagina. Careful inspection of the vestibule failed to reveal an ectopic ureteral orifice. Physical findings, including rectal examination, were otherwise negative.

The catheterized urine was clear (specific gravity 1.020), contained no albumin or sugar, was negative microscopically, and sterile on culture. The blood urea nitrogen was 14 mg. per cent; the blood Mazzini was negative. The blood count was normal.

Excretory urography disclosed both kidneys were normal in size, shape, and position. Good renal function was present on both sides. The calyces and renal pelvis of each kidney were of normal configuration. Only the lower portion of the left ureter was visualized and appeared normal. There was no outline of a right ureter. The cystogram was normal. Nothing in the pyelogram on either side suggested reduplication of the renal pelvis or ureter (fig. 1, *A*).

At cystoscopy, under ether anesthesia, the bladder mucosa was normal and a normal ureteral orifice was seen in its usual location on either side of the trigone. Intravenous indigo carmine returned from ureteral orifices in 5 minutes with excellent concentration. No indigo carmine could be seen in the urine draining from the vagina. Ureteral catheters were introduced into several folds in the vagina which had the appearance of possible ectopic ureteral orifices, but on x-ray checkup none of these suspicious folds proved to be a ureteral orifice. Vaginoscopy was then performed, employing both 16F Brown-Buerger and McCarthy baby cystoscopes. Normal-appearing vaginal mucosa and a normal cervix were visualized, but nothing suggestive of a ureteral orifice could be seen in any portion of the vagina or cervix, nor was there any excretion of indigo carmine visible.

A vaginogram was made, with the patient in Trendelenburg position and the vagina distended with 20 cc 40 per cent hippuran. X-ray clearly demonstrated reflux of the medium into an ectopic ureter which apparently drained into the right lateral fornix of the vagina. The ureter was of normal caliber and was outlined to the level of the lower pole of the right kidney; neither the corresponding renal pelvis nor calyces were visualized (fig. 1, *B*). By means of the vaginogram we were thus able to definitely establish the presence of an ectopic vaginal ureter which led from the right kidney.

Operation was performed several days later, under inhalation anesthesia.

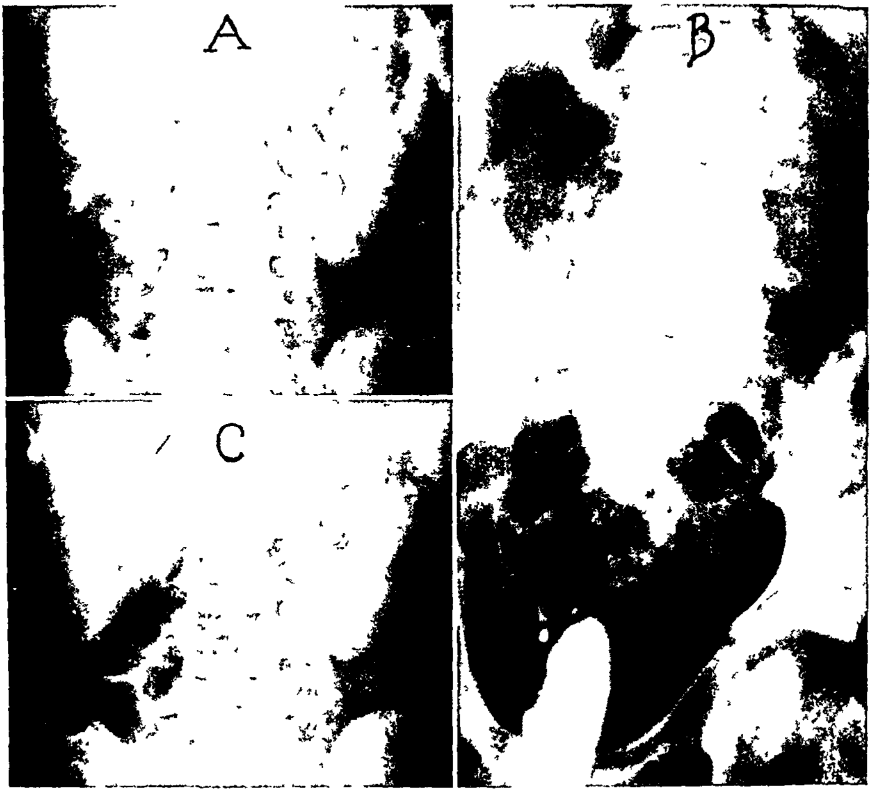

FIG. 1. *A*, preoperative excretory urogram revealing no suggestion of reduplication of right renal pelvis or ureter *B*, vaginogram showing reflux up ectopic right ureter *C*, excretory urogram 3 months after right heminephrectomy showing normal pyelogram.

Cystoscopy was first done, and for the purpose of its identification at operation a 4F ureteral catheter was passed up the right ureter which drained into the bladder. The right kidney was exposed through a lumbar, extraperitoneal incision; it was found to be of the double type, with reduplication of both the renal pelvis and ureter. The superior pole of the kidney was very adherent to the adrenal gland, requiring sharp dissection for mobilization. Each segment of the kidney had its own well-developed vascular pedicle. The upper pelvis was rudimentary, but the lower pelvis was well developed. Both ureters were normal in appearance; the one leading to the bladder, which was readily identified by the indwelling catheter, drained the lower pelvis, and the ectopic vaginal ureter drained the upper pelvis. The superior segment of the kidney was small and well demarcated from the much larger inferior segment by a pronounced indentation on the surface of the kidney; the parenchyma of both segments was grossly normal. The ureter draining the upper pole of the kidney was freed to the lower angle of the wound, where it was clamped, severed, and ligated. The pedicle of the superior segment of the kidney was doubly clamped, cut, and ligated. The upper pole of the kidney was then excised by making a wedge-shaped incision through the indented zone between the segments, and the raw surfaces of the kidney approximated with several interrupted fine chromic catgut sutures. Hemostasis was excellent.

Histological examination of the excised superior pole of the kidney revealed well-spaced, normal-appearing glomeruli, the tubules showed slight cloudy swelling of the lining cells, but were otherwise normal

The postoperative course was uneventful, the wound healed per primam without urinary drainage from it at any time, and all urinary leakage from the vagina promptly stopped The patient was discharged from the hospital 10 days after heminephrectomy

Excretory urography 3 months later revealed a normally-functioning right kidney with normal configuration of the calyces and renal pelvis (fig 1, *C*) No symptoms were referable to the urinary tract The urine was normal

SUMMARY

The diagnostic difficulties in vaginal ectopic ureter are discussed The use of the vaginogram to demonstrate ureteral reflux is suggested A case is reported illustrating the value of this procedure

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BILATERAL URETERAL OBSTRUCTION DUE TO CHRONIC INFLAMMATION OF THE FASCIA AROUND THE URETERS

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From Kaiser Foundation Hospital, Oakland, Calif.

Seven cases of bilateral ureteral obstruction due to chronic inflammation of the fascia surrounding the ureters have been reported.[1-5] It is our purpose to add an eighth case of this little described entity.

CASE REPORT

H. R., PF No. 335220, a 36 year old white man, was admitted to the medical out-patient clinic on August 14, 1952 because of swelling of the legs and genitalia of one week's duration. He also complained of nausea and vomiting, and 2 to 3 loose, watery, bowel movements per day.

His past history revealed that he had colitis, first diagnosed in 1943. He had a relapse in 1947 of six weeks' duration and a second recurrence of his colitis in January 1952 which persisted until the date of his admission to the hospital. His symptoms consisted of a 15 pound weight loss in the past 6 months, and of frequent bloody, mucoid, watery stools, often as frequent as 10 times a day. A barium enema done in our out-patient clinic was considered consistent with the diagnosis of ulcerative colitis. In January 1952 he began to lose his libido and the patient claimed that he had been impotent for 3 months prior to his hospital admission.

His physical examination was negative except for a blood pressure of 160/95 and 2 plus edema of the ankles and scrotum, and 1 plus edema of the sacral area.

Laboratory work-up revealed blood hemoglobin 10.5 gm.; red blood cells 3.05 million; white blood count 6,200 with 79 per cent neutrophiles, 20 per cent lymphocytes and 1 per cent eosinophiles. The sedimentation rate was 40 mm/hr. (Westergren), nonprotein nitrogen 100 mg. per cent, blood urea nitrogen 58 mg. per cent, plasma creatinine 6.5 mg. per cent, chloride 110 m/Eq., carbon dioxide combining power 29 m/Eq. The total protein was 7.9 gm. with 4.3 gm. of albumin and 3.6 gm. of globulin. The urine showed a specific gravity of 1.018; pH 5.0; albumin 0, sugar 0, with an occasional white blood cell and an occasional epithelial cell.

The patient was admitted with a tentative diagnosis of nephrotic stage of glomerulonephritis or intra-abdominal venous obstruction. One of the observers from the cardiovascular department believed that he could palpate the kidneys bilaterally and suggested a diagnosis of polycystic renal disease or a chronic

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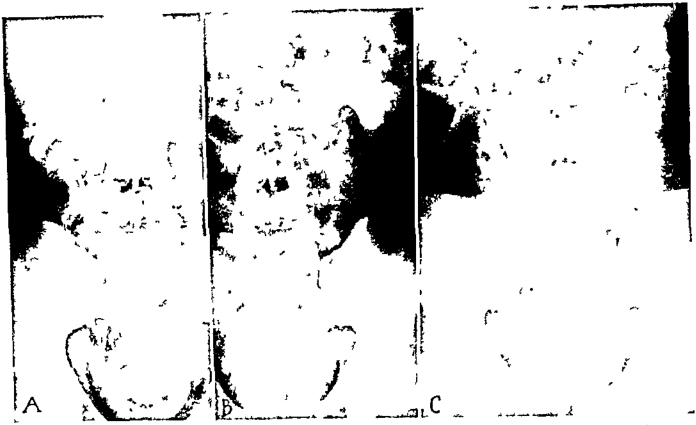

FIG. 1. *A*, right retrograde pyelo-ureterogram, preoperative. *B*, left retrograde pyelo-ureterogram, preoperative. *C*, bilateral retrograde pyelo-ureterogram, 6 months postoperative

bilateral ureteral obstruction of undetermined cause. A urological consultation was requested.

The cystoscopic examination was normal. The right ureteral orifice was catheterized with ease and 55 cc of grossly clear urine was obtained. Pyelography (fig. 1, *A*) revealed a markedly hydronephrotic right kidney. Indigo carmine injected intravenously failed to appear from either the catheter in the right ureter or from the left ureteral orifice in 30 minutes. The left ureteral orifice proved difficult to catheterize, and efforts to accomplish this were abandoned because of the fear of a reflux anuria. Two days later a right nephrostomy and a right ureterolysis were done. The ureter was found to be obstructed from the renal pelvis to the promontory of the sacrum by a thick, coarse, fibrous sheath which seemed to originate from the fascia of the psoas muscle laterally, and to extend across the ureter and to disappear over the vertebral bodies medially. The uppermost part of this fascial sheath was compressing and partially obstructing the renal pelvis. The remainder of the sheath was partially obstructing and compressing the ureter and pulling it to a position much more medial than normal. This fascial sheath was opened along its lateral margin, that is, at the point at which it seemed to fuse with the fascia of the psoas muscle, and lifted upward to expose the ureter lying underneath it. The ureter itself seemed to be enmeshed in a dense matrix of scar tissue even after the fascial sheath had been freed. The ureter was dissected from this scar tissue bed from the renal pelvis to a point well below the promontory of the sacrum, and when freed, it came to lie in a more lateral and normal course. Palpation of the ureter, thus freed, revealed some induration along its course as though its walls had been infiltrated with scar tissue. Biopsy of the fascial sheath and the scar matrix in which the ureter was imbedded revealed chronic inflammatory tissue. Postoperatively, the patient did well and he was discharged from the hospital 9 days after his operation with a nephrostomy tube indwelling in the right kidney. His blood chemistry at the time of discharge was essentially normal.

He was re-admitted on September 23, 1952 and a catheter was passed to the left kidney. One hundred and five cc of clear urine was aspirated from the pelvis of the left kidney. This urine contained Proteus by culture. Pyelograms and ureterograms (fig.1, *B*) revealed a situation similar to that previously described on the right side. On October 1, 1952 a left nephrostomy and ureterolysis were done. The situation encountered at operation was essentially the same as that described on the right side except that after the left ureter was freed even more areas of induration could be palpated within the wall of the ureter. The patient made a good recovery from his second operation and both nephrostomy tubes were removed.

Three weeks following the second operation the nonprotein nitrogen was 39 mg. per cent and the creatinine 1.42 mg.

The patient has been followed carefully since the operations for a period of 12 months. During this time he was able to resume his work as a painter, and has been well except for two episodes of chills and fever which responded rapidly to aureomycin therapy. Retrograde studies (fig. 1, *C*) 6 months postoperatively revealed an essentially normal right kidney with good function and good emptying. On the left side hydronephrosis is still present, but less marked than preoperatively. Function from both kidneys is excellent, but the emptying of the left kidney is still delayed. Interestingly enough, libido returned soon after discharge from the hospital. The patient is being followed in the clinic, and on his last visit, one year after his original hospitalization, he was well, working, and his blood chemistry continued to be normal.

DISCUSSION

It is well known that inflammatory conditions of the bowel can cause urological complications. Ureteral obstruction due to regional ileitis has been reported by Hyams, et al.,[6] Ginsberg and Oppenheimer,[7] Redish[8] and others. Ureteral obstruction due to appendicitis has been reported by Trabucco and Marquez,[9] Hughes,[10] and others. Harlin and Hamim[11] reported cases of diverticulitis of the colon as well as extraperitoneal appendicitis and regional ileitis as causes of ureteral obstruction. We could find no reference in which ulcerative colitis was considered to be the cause of ureteral obstruction. Since our patient had a 10-year history of symptoms suggestive of ulcerative colitis and x-ray evidence to support the diagnosis, one cannot help but wonder if there is any correlation between the two conditions, at least in the case presented.

The excellent anatomical studies of Daseler and Anson[12] demonstrate the

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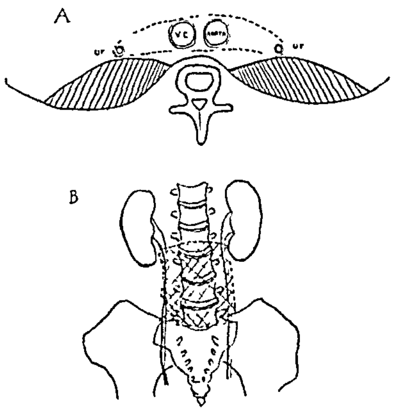

Fig 2 *A*, cross section through level of L4 showing intermediate layer of retroperitoneal fascia surrounding vena cava, aorta and ureters Para-aortic lymph nodes are enclosed within this sheath *B*, extent of involvement

existence of a retroperitoneal fascia which encloses the abdominal aorta and vena cava along with both upper urinary tracts within one potential space (fig. 2, *A*). The para-aortic lymph nodes, which drain the bowel, are adjacent to the aorta and thus lie within this potential space (fig. 2, *B*). Any inflammatory disease of the bowel could reach this space by way of the lymphatics. In our case we had the opportunity to examine each lateral border of the inflammatory mass from the retroperitoneal exposure and found the ureters to be enclosed within the inflammatory tissue and drawn medially. We cannot be certain that the great vessels were also enclosed within this fibrous tissue. Bradfield,[5] however, explored a similar case transperitoneally and found that the inflammatory mass "obscured the bifurcation of the aorta." Postulating such a space infection would account admirably for the situation found at operation in our case. Also it would account for the edema of the leg and sacrum and genitalia (which was the chief complaint at the time of hospital admission) by compression of the inferior vena cava

Those of us who have been confronted with the problem of ureteral obstruction due to retroperitoneal inflammatory disease have proceeded with the treatment by instinct as the number of reported cases are too few to establish a best method of treatment. In some cases nephrectomy had been done on the more involved side,[2, 3] others have obtained good results by resecting the inflamed bowel,[6, 8] still other urologists had chosen nephrostomy[1-3] and/or ureterolysis,[1, 5, 13] One case was reported in which simple indwelling ureteral catheters was the only treatment.[4] In the case reported here, a combination of nephrostomy and ureterolysis was employed. In some cases the surgical approach has been transperitoneal, and in others retroperitoneal. Another form of treatment which has

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cidedly discouraging, largely due to the fact that the growth has already metastasized although in the gross it appears well circumscribed. Soloway states that of the 149 reported cases in which operation was performed there are only 32 patients who were followed and reported as well. It would appear, therefore, that considerably more time and effort should be exerted in the direction of early diagnosis and treatment of a condition which presents such a high degree of malignancy and where the reported incidences of cures is so very low.

SUMMARY

A case of primary carcinoma of a ureteral stump, presenting 3½ years after a nephrectomy and partial ureterectomy, is recorded. The diagnostic criteria of this condition are also discussed. This is the second case on record.

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WAR INJURIES OF THE LOWER URINARY TRACT AND MALE GENITALIA

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The war in Korea has added another chapter in the annals of military medicine The mortality rate in our military hospital units has been the lowest in any war Wound infections postoperatively have been reduced to a minimum This has been brought about by the excellent means of evacuation of the wounded, early adequate surgery near the forward areas, the liberal use of blood, antibiotics and other tools of modern medicine

The accumulated experiences of the medical officers who handled the casualties in previous wars have enabled us to treat our wounded in the most efficacious manner This paper relates our experience in handling war wounds of the lower urinary tract and male genitalia

The cases presented herein were treated in the U. S Naval Hospital aboard the U S S Repose (AH-16) during its stay in Inchon from July 1952 to January 1953

INJURIES OF THE URINARY BLADDER

Bladder injury should be suspected in all wounds of the lower abdomen, buttocks, hips, upper thighs, and external genitalia The urine should be examined in all such cases before initial surgery is carried out If the patient is unable to urinate, he should be catheterized

Injury to the bladder is characterized by hematuria, lower abdominal pain, tenderness and rigidity The symptoms and signs of an acute abdomen can be caused either by the bladder injury or the associated injury of abdominal viscera It is possible to have a perforating injury of the bladder without the symptoms and signs of an acute abdomen One of the cases presented below will illustrate this point

If bladder injury is suspected, a retention catheter should be inserted and bladder drainage carried out In small perforating injuries, this may be the only treatment necessary, it will do much to prevent further urinary extravasation with contamination of prevesical space and peritoneal cavity The diagnosis can be definitely made by cystoscopy or cystograms The former was preferred

The treatment of most bladder injuries requires exploration of the prevesical space and of the bladder It is preferable to repair the perforations by suturing the serosa and the muscularis, but in the region of the trigone and other places where the serosa is not readily accessible, it is necessary to place sutures through the mucosa of the bladder in order to effect a repair The prevesical and paravesical spaces should be drained and a cystostomy tube left in place

An abdominal exploratory should be carried out in all bladder injuries requiring surgery, for in the majority of instances, there will be associated injury to an abdominal viscus (table 1)

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TABLE 1. *Injuries of the urinary bladder*

Case	Wound Entrance	Clinical Findings	Condition of Patient Preop.	Urinary Tract Injuries	Associated Visceral Injuries	Treatment of Urinary Tract Injury	Condition Postop.
1	Rt. buttock	Hematuria	Good	Perforation of bladder	None	Cystostomy and suture of bladder wound 5 days post-injury	Good
2	Rt. hip	Hematuria; tenderness and rigidity of lower abdomen; suprapubic hematoma	Good	Perforation of anterior portion of bladder neck	None	Cystostomy and suture of bladder wound. Wide drainage.	Good
3	Lt. hip	Hematuria; tenderness and rigidity of lower abdomen	Good	Perforations of lt. lateral and post. walls of bladder	None	Cystostomy and suture of bladder perforations. Wide drainage.	Good
4	Lt. post. thigh	Hematuria Acute abdomen	Fair	Perforations of lt. lat. wall and dome of bladder	Perforating wounds of ileum and sigmoid	Cystostomy and suture of bladder perforations. Wide drainage.	Good
5	Lt. and rt. buttocks	Hematuria Acute abdomen	Critical	Two perforations of post. wall of bladder	Perforations of ileum	Penile catheter drainage.	Fair; eventual recovery

CASE REPORTS

Case 1. A 23 year old 2nd Lt., USMC, hit by shrapnel, sustained a wound of the right buttock. Urine was grossly bloody. Examination revealed the patient to be in good condition. His abdomen was soft and nontender. An x-ray revealed a metallic foreign body in region of the urinary bladder. Cystoscopy revealed a small piece of shrapnel in the bladder. The perforation was on the right posterolateral wall. The ureters were catheterized and found to be intact. A Foley catheter was inserted per urethram into the bladder and the patient was observed.

The patient did well for 3 days. On the third day, urine leaked through the buttock wound. This continued despite catheter drainage. The bladder was explored through a low midline incision. The prevesical space was hemorrhagic. The metallic foreign body was removed from the bladder and the perforation repaired with interrupted sutures taken through the mucosa and muscularis. A cystostomy tube was left in place and the prevesical space drained. The patient did well postoperatively. The drains were removed in 6 days and the cystostomy tube in seven. The remainder of his postoperative course was uneventful.

Case 2. A 23 year old corporal, USMC, hit by a sniper's bullet, sustained wounds of the right hip and left side of the scrotum. The patient was brought to this hospital by helicopter. Upon examination, the wound of entrance was seen on the right hip and the wound of exit in the upper portion of the left side of the scrotum. There was a suprapubic hematoma with tenderness and rigidity of the lower abdomen. The urine was grossly bloody. An x-ray revealed a chip fracture of the neck of the right femur.

The patient was explored through a Pfannenstiel incision. Both rectus muscles were cut to obtain adequate exposure. The prevesical fascia and adipose tissue were hemorrhagic. A perforation of the bladder was located at the anterior portion of the bladder neck. The puboprostatic ligaments were torn and the symphysis pubis shattered. The bladder was opened and bone fragments were removed. Hemostasis was carried out. The intramural portion of the ureters was intact and no other wounds were found. The bladder was closed with interrupted and continuous 00 chromic sutures taken through serosa and muscularis. The cystostomy tube was left in place. A Foley catheter with a 30 cc bag was inserted into the bladder per urethram. After the bag was filled, the catheter was placed on tension. The peritoneum was opened and abdominal viscera examined. There was no injury of an abdominal viscus. No perforations of the pelvic peritoneum were noted. The prevesical and paravesical spaces were drained after the peritoneum was closed. Closure was carried out in the usual fashion. The left side of the scrotum was explored; there was no damage to the testicle or cord.

The postoperative course was favorable. The urethral catheter was left on tension for 48 hours and was removed on the fifth postoperative day. The cystostomy tube was removed on the eighth postoperative day. The patient was evacuated to the rear area in good condition.

TABLE 1. *Injuries of the urinary bladder*

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5	Lt. and rt. buttocks	Hematuria Acute abdomen	Critical	Two perforations of post. wall of bladder	Perforations of ileum	Penile catheter drainage.	Fair; eventual recovery

Case 5 A 25 year old Korean Marine, hit by enemy burp gun fire, sustained wounds of both buttocks He was brought to this hospital by helicopter in critical condition Upon examination, his blood pressure was 112/78, pulse was 114 and his abdomen was distended, tender, and rigid Urine was grossly bloody and the rectum contained blood and feces An x-ray revealed fracture of L-5 with the missile lying in the left iliac area

The patient was explored through a left rectus incision Marked fibropurulent peritonitis was noted Three large perforations of the ileum were sutured in two layers with 00 chromic catgut The wound of entry into the peritoneum was to the left of the rectosigmoid A drain was placed in the region of the left ureter as injury to the ureter was expected A complete exploratory of the bladder and ureter could not be done as patient's condition did not permit His abdomen was closed with through and through interrupted stainless steel sutures A urethral catheter was left in the bladder as injury to that organ was suspected

Upon removal of the urethral catheter on the fifth postoperative day, the patient did well Four days later, on the ninth postoperative day, urine leaked from the abdominal incision A catheter was re-inserted At cystoscopy, 12 days postoperatively, two perforations of the bladder were noted, one at the interureteric ridge near the right ureteral orifice and the other in the posterior wall of the bladder The ureters were catheterized and found to be intact A urethral catheter was left in for ten more days No urinary leakage followed its removal The bladder had apparently healed

Comment A number of cases have been sent to us postoperatively in which suspected bladder injury was treated by a retention catheter In most of these, the patient's condition did not permit exploration of the bladder along with other surgical procedures After leaving the catheter in place for about 10 days it was found that urinary extravasation did not take place and that apparent healing had resulted One patient passed a piece of shrapnel per urethram following the removal of the catheter, he experienced no further difficulty with the exception of dysuria and frequency for about four days after the metal had passed These cases illustrate the salient points in the treatment of bladder injury, namely, the drainage of the prevesical and paravesical spaces putting the bladder to rest The extent and nature of the injury will be the determining factor with regard to whether or not an open repair is necessary

INJURIES OF POSTERIOR URETHRA

This type of injury presents special problems to the urologist as it has a tendency to cause stricturing of the posterior urethra Close follow-up care is necessary if the patient is to have a relatively normal urinary tract

Injury to the posterior urethra should be suspected in every case of fractured pelvis The initial symptoms may be urinary retention following injury, hematuria, or those similar to bladder injury If the urethra is completely severed distal to the bladder neck, the patient will usually suffer urinary retention There may also be urinary extravasation into the prevesical space with the symptoms and signs of an acute abdomen

Case 3. A 22 year old private first class, USMC, hit by burp gun fire, sustained wounds of the left hip and buttocks. The patient was brought to this hospital by helicopter. On examination, there was one wound of the left hip and one wound of each buttock. The lower abdomen was tender and rigid. Urine was grossly bloody. An x-ray revealed the metallic foreign body to be lodged to the right of symphysis pubis somewhere in the perineum.

An exploratory operation was done through a low left rectus incision. The prevesical space was full of blood. The bladder was opened, wound of entrance located in left lateral wall of bladder, wound of exit in right half of trigone below right ureteral orifice. The latter perforation was sutured interruptedly through the mucosa and muscularis. The wound of lateral wall was closed by interrupted suturing of serosa and muscularis. The bladder was closed with interrupted and continuous suture in two layers. A cystostomy tube was left in place.

The peritoneal cavity was explored and there was no damage to other abdominal viscera. The prevesical and paravesical spaces were drained. Closure was carried out in the usual fashion. Other wounds were debrided and drained. A urethral catheter was left in place.

Postoperatively, the patient did well. The urethral catheter was removed in 4 days. Five days postoperatively, the patient voided bloody urine but passed clear urine through the cystostomy tube. Seven days postoperatively, he was voiding clear urine. The cystostomy tube was left in place as the patient was being evacuated to a hospital in Japan.

Case 4. A 13 year old Korean boy, hit by burp gun fire, sustained a wound of the left thigh posteriorly. He was sent to this hospital by helicopter. On examination, his entire abdomen was tender and rigid. Urine was grossly bloody. An x-ray revealed the bullet to be lodged in the pelvis at the level of the promintory of the sacrum.

A laporotomy was carried out through the right rectus incision. The peritoneal cavity was full of blood. There were multiple perforating wounds of the ileum and sigmoid. The former were closed with a double layer of interrupted and continuous 00 chromic sutures. The latter were closed in a similar manner and damaged portion of the sigmoid was exteriorized. The prevesical space was explored and the bladder opened. The wound of entrance was in the left lateral wall of the bladder and the wound of exit near the dome. Both wounds were closed by means of interrupted sutures taken through the serosa and muscularis. The bladder was closed by means of interrupted and continuous suture. A cystostomy tube was left in place. Drains were left in the prevesical and paravesical spaces and peritoneal cavity. The exteriorized portion of sigmoid was brought out through a left McBurney incision. Closure was carried out in the usual fashion.

The postoperative course was stormy as the patient had convulsions, abdominal distention and high temperature. With each convulsion, he passed an Ascaris through the nose or mouth. The colostomy was opened in forty-eight hours and there was improvement from then on. The patient was transferred to an Army hospital 6 days postoperatively in favorable condition.

Case 5. A 25 year old Korean Marine, hit by enemy burp gun fire, sustained wounds of both buttocks. He was brought to this hospital by helicopter in critical condition. Upon examination, his blood pressure was 112/78, pulse was 144 and his abdomen was distended, tender, and rigid. Urine was grossly bloody and the rectum contained blood and feces. An x-ray revealed fracture of L-5 with the missile lying in the left iliac area.

The patient was explored through a left rectus incision. Marked fibrouprulent peritonitis was noted. Three large perforations of the ileum were sutured in two layers with 00 chromic catgut. The wound of entry into the peritoneum was to the left of the rectosigmoid. A drain was placed in the region of the left ureter as injury to the ureter was expected. A complete exploratory of the bladder and ureter could not be done as patient's condition did not permit. His abdomen was closed with through and through interrupted stainless steel sutures. A urethral catheter was left in the bladder as injury to that organ was suspected.

Upon removal of the urethral catheter on the fifth postoperative day, the patient did well. Four days later, on the ninth postoperative day, urine leaked from the abdominal incision. A catheter was re-inserted. At cystoscopy, 12 days postoperatively, two perforations of the bladder were noted, one at the interureteric ridge near the right ureteral orifice and the other in the posterior wall of the bladder. The ureters were catheterized and found to be intact. A urethral catheter was left in for ten more days. No urinary leakage followed its removal. The bladder had apparently healed.

Comment. A number of cases have been sent to us postoperatively in which suspected bladder injury was treated by a retention catheter. In most of these, the patient's condition did not permit exploration of the bladder along with other surgical procedures. After leaving the catheter in place for about 10 days it was found that urinary extravasation did not take place and that apparent healing had resulted. One patient passed a piece of shrapnel per urethram following the removal of the catheter, he experienced no further difficulty with the exception of dysuria and frequency for about four days after the metal had passed. These cases illustrate the salient points in the treatment of bladder injury, namely, the drainage of the prevesical and paravesical spaces putting the bladder to rest. The extent and nature of the injury will be the determining factor with regard to whether or not an open repair is necessary.

INJURIES OF POSTERIOR URETHRA

This type of injury presents special problems to the urologist as it has a tendency to cause stricturing of the posterior urethra. Close follow up care is necessary if the patient is to have a relatively normal urinary tract.

Injury to the posterior urethra should be suspected in every case of fractured pelvis. The initial symptoms may be urinary retention following injury, hematuria, or those similar to bladder injury. If the urethra is completely severed distal to the bladder neck, the patient will usually suffer urinary retention. There may also be urinary extravasation into the prevesical space with the symptoms and signs of an acute abdomen.

If the patient is unable to urinate following injury to the pelvis, he should be catheterized. If the posterior urethra has been injured, gross blood will be seen to pass through the catheter when the damaged area has been reached. If one is able to insert the catheter into the bladder, the urine will usually be grossly clear. In more severe posterior urethral injuries, it will not be possible to catheterize the bladder.

The treatment will, of course, depend on the extent and nature of the injury. If the urethra has not been completely severed and no extravasation has taken place, a retention catheter should be left in place. It is usually necessary to leave the catheter in about seven or eight days. It is very important that the urethra be dilated following the removal of the catheter. The frequency of dilatation will depend on the size and force of the urinary stream during the patient's convalescence. It is usually necessary to dilate the urethra at weekly intervals for two to three weeks. The interval can then be gradually prolonged until dilatation will no longer be required.

Surgery is required when the urethra has been severed or when urinary extravasation has taken place. It is usually impossible to catheterize these patients. An approach similar to that used in retropubic prostatectomy is preferable. The urethra and bladder should be approximated after a cystostomy has been carried out. This may entail the use of "male" and "female" sounds, retrograde catheterization, or other techniques with which the urologist is familiar. A 22F or a 24F Foley catheter with a 30 cc bag is left in place. The prevesical space should be drained adequately. The urethral catheter may be placed on traction for two or three days.

There has been some recent work which indicates that cortisone used postoperatively will prevent formation of excessive scar tissue and subsequent stricture formation. We used this in one case, but unfortunately the treatment was discontinued when the patient was evacuated to Japan.

Case 1. A 28 year old Korean Marine sustained a fractured pelvis upon being struck by a truck. He was brought into this hospital by helicopter. X-ray of the pelvis revealed a linear fracture through the left side of the sacrum with displacement superiorly. There was also a transverse fracture of both pubic rami with rotation and twisting of the pubis.

Upon examination, patient was found to have tenderness and rigidity of the lower abdomen. An attempt at catheterization yielded only gross blood when the posterior urethra was reached.

The patient was taken to the operating room where blood was given until the patient was out of shock. The bladder and prostate were exposed through a low midline incision. Much blood was evacuated from the prevesical space. The bladder was opened and about 400 cc of clear urine was removed. Further examination revealed a tear of posterior urethra just distal to bladder neck. The prostatic urethra was full of blood. A 24F Foley catheter was passed into the bladder on a mandarin by guiding it through the damaged posterior urethra. The Foley bag was distended with 25 cc water and the catheter placed on traction. A cystostomy tube was left in place and the prevesical space drained.

The postoperative course was completely satisfactory. The urethral catheter was changed and the urethra dilated to 24F eight days postoperatively. The cystostomy tube was removed at that time. The urethral catheter was removed twelve days postoperatively. A 24F sound was passed with ease. Fourteen days postoperatively, patient urinated normally. He was then evacuated to another hospital.

The patient was again seen in this hospital about six weeks after initial surgery. He had not been followed by urethral dilatations. He was having difficulty urinating, and his stream was small. He was dilated again to 28F with ease; follow-up continued until patient was evacuated.

Case 2. A 22 year old Marine, hit by enemy burp gun fire, sustained a wound of the left thigh. He was brought to this hospital by helicopter. An attempt to catheterize him at a Marine medical company yielded gross blood.

Upon examination, the wound of entrance was observed on the left thigh. The missile could be palpated just under the skin of the lateral aspect of the right buttock. He was unable to dorsiflex his right foot and hypoesthesia was present on the dorsum of the left foot. Rectal examination was negative.

X-ray of the pelvis revealed fracture of inferior pubic rami.

The patient was taken to the operating room where an attempt was made to insert a catheter. Gross blood was obtained when the posterior urethra was reached. Another attempt was made to insert a Foley catheter by means of utilizing a mandarin. This was successful, and clear urine was obtained from the bladder. The wound was debrided and the bullet removed from right buttock. The catheter was placed on slight tension and taped to the thigh.

The catheter was removed 7 days postoperatively. Four days after removal of the catheter, the patient noted a decrease in the size of his urinary stream with difficulty in voiding. The urethra was then dilated to 24F by means of a Le Fort sound passed on a filiform, and a Foley catheter was re-inserted.

The patient was then started on 100 mg. of cortisone per day after blood chemistries, electrocardiograms, weight, etc., had been checked. The catheter was removed 4 days later and the urethra was dilated to 24F.

The patient required no further dilatations for 10 days after which time he was transferred to a Naval Hospital in Japan. It was intended that the patient be kept on cortisone for three to four weeks, but he was evacuated before treatment could be completed. When last seen in Japan, he was voiding well.

Comment. The use of cortisone for the prevention of urethral stricture may alter the post-injury course of urethral and ureteral injuries. The present results of urethral surgery with its subsequent stricture formation are far from satisfactory. More work along this line will be required before any definite conclusions can be reached.

INJURIES OF THE PENIS, SCROTUM AND TESTICLES

These injuries were most often seen in conjunction with multiple injuries of the extremities. The surgical treatment of penile wounds was handled somewhat differently in that debridement was followed by primary closure. Secondary suture was not required in any case. The good results obtained by this method was most likely due to the liberal use of antibiotics.

All penetrating wounds of the scrotum required scrotal exploration to determine the extent of injury to the testicle. Any testicular tissue which was believed viable was preserved. A testicle was removed only if it was completely destroyed. At times, this necessitated the reconstruction of the tunica albuginea; but the results warranted the undertaking of such a painstaking procedure.

A drain should be left in the scrotum following every scrotal exploratory. This simple procedure reduces and often prevents a scrotal hematoma which would have resulted from the injury. In cases in which a hematoma was present prior to surgery, scrotal drainage is the best method of treatment.

Of some twenty consecutive cases of testicular injury, orchiectomy (unilateral) was required in seven. We have seen only one emasculating injury during our entire tour of duty in Korea. It is hoped that these injuries will be entirely prevented by the use of genitalia "armor."

SUMMARY

A review of war injuries of the lower urinary tract and male genitalia, as seen in the U. S. Naval Hospital in the U.S.S. Repose (AH-16), has been presented in the hope that these experiences will be of value to those doing traumatic surgery.

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PSEUDO-EXSTROPHY OF BLADDER

JAMES H HEJTMANCIK, WALTER B KING AND MORETON A MAGID

Congenital exstrophy of the urinary bladder has been defined as a malformation found in both sexes, in which the anterior wall of the bladder and that portion of the anterior abdominal wall over it are missing, so that the inner surface of the posterior wall of the bladder protrudes on the abdomen and the ureters expel urine externally Usually no attempt is made to classify congenital exstrophy of the urinary bladder further Classical exstrophy of the bladder is relatively rare, being said to occur approximately once in every 30,000 to 40,000 births, and is more common in males in about a ratio of five to one

In the female, the clitoris is cleft, and the labia rudimentary. The urethra appears as an open sulcus or groove in the classical case In some cases, there are abnormalities of the vagina Sometimes the lower third of the anterior vagina is missing, and in some cases, there is a double vagina The uterus may be normal, absent, or bicornate In the male, a short rudimentary penis is usually present with a complete epispadias Occasionally the scrotum is bifid The bodies of the pubic bones are usually widely separated which is said to give the patient an unstable pelvis and consequently a waddling gait. There is also usually no umbilical depression in the abdominal wall Along with the aforementioned abnormalities, associated anomalies are frequently found, the most common of which are inguinal hernia, imperforate anus, undescended testicles, and spina bifida

It is notable in the literature that very little attempt has been made to classify exstrophy of the bladder further, probably because variations from classical exstrophy are uncommon Babcock states that there are two rarer forms of exstrophy for which the intestinal transplantation of the ureters is not adapted The first is the superior type of exstrophy, in which the neck of the bladder and urinary sphincters are not involved, and plastic closure may be all that is needed The other is the inferior type of exstrophy, in which there is no anal control, and therefore diversion of the urine to the colon is unthinkable McKenzie described a patient who had a "split pelvis," but had no bladder exstrophy For obstetrical indications, the patient required a cesarean section The bladder was found under the skin of the abdominal wall incorporated into the anterior abdominal fascia Higgins reported a case in which the symphysis was intact and a normal penis was present with an otherwise complete exstrophy of the bladder It has been recognized that this type of embryonic maldevelopment can vary from a very mild form which requires simple correction to the extreme anomalies which are incompatible with life

The cause of exstrophy is unknown One common belief is that it is due to a failure of mesodermal masses to fuse in the midline leaving a deficient abdominal wall Others believe that there is a complete failure of all three layers, entoderm, mesoderm and ectoderm to fuse in the midline We wish to add another case

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of the mild form of this congenital anomaly in which the treatment was relatively simple.

CASE REPORT

R. V., a 7-year old Mexican girl, was first seen in October 1952. Since birth, her mother had noticed a "bulge" on her lower abdominal wall. The mass would increase on straining of any type. Urinary function and control had been normal since birth. She had no complaints as to frequency or repeated urinary tract infections. The child had not started to school because her mother was afraid some injury might occur to this herniated mass. Her review of systems, past history, and family history were otherwise essentially negative.

Blood pressure, temperature, pulse and respiration were normal. Heart and lungs were normal. On examination of the abdomen, the umbilicus was absent. There was a wide defect of the recti muscles, through which bulged a soft round mass (fig. 1, A and B). This mass was covered in its superior half by what appeared to be normal skin. In the inferior half, the skin was fused to what appeared to be an epithelization of the anterior wall of the bladder. The surface in this area was irregular and scarred. The lateral margins of this herniated mass felt as if they were continuous with the rectus fascia. On palpation, there

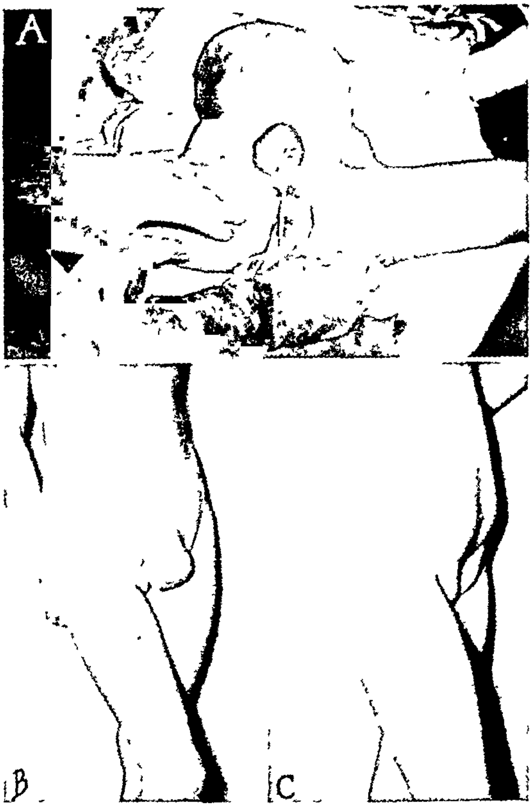

FIG. 1. *A*, preoperative photograph revealing cleft clitoris, rudimentary labia and separation of pubic bones. *B*, preoperative photograph showing herniated bladder and separation of rectus muscles. *C*, postoperative result using stainless steel mesh for re-inforcement.

was a wide separation of the pubic bones On vaginal examination, the clitoris was cleft, and there was a moderate separation of the labia The urethra and vagina were otherwise normal except for a small polyp at the vaginal orifice It was significant that this patient did not have a waddling gait

Laboratory studies were all within normal range Excretory urography showed a normal upper urinary tract with wide separation of the pubic bones Cystoscopy under anesthesia revealed a normal bladder and urethra Bladder capacity was approximately 200 cc Upon distending the bladder, it could be easily ascertained that the protruding mass was the urinary bladder The inferior half of the anterior bladder wall was extremely thin and would transilluminate during cystoscopy As far as could be ascertained, the vagina and uterus were normal The remainder of the examination was negative

With the bladder distended with sterile water, the lateral bladder wall was freed from its fusion with the rectus fascia The normal appearing skin over the superior half of the bladder was removed The abnormal epithelium covering the inferior half of the bladder was left undisturbed and buried with the bladder because of danger of perforating the extremely thin anterior bladder wall in this area Following this, the bladder could be easily replaced in the normal position The peritoneum was not opened The rectus muscles could not be approximated, so flaps of the anterior rectus sheaths were used to close the defect External to this closure, a stainless steel mesh was placed for re-inforcement Because of the mild abnormality of the vulva, it was not thought necessary to do a plastic repair at this time Her postoperative course was uneventful, and except for a small amount of serous drainage early in the convalescence, the wound healed firmly At the present time, the child is going to school and enjoying normal activity The abdominal closure had remained firm with no ill effects from the steel mesh (fig 1, *C*)

DISCUSSION

Although this case is a very mild form of the abnormalities associated with exstrophy of the bladder, it is interesting because of its uncommon occurrence It gives rise to some speculation as to the increased likelihood of adenocarcinoma of the bladder in this patient Malignant change may occur in exstrophy of the bladder either from a congenital predisposition or from long years of infection and trauma to the exposed bladder Some investigators believe that the presence of glandular tissue in the bladder is due to cell inclusion while others suggest that adenocarcinoma may originate in remnants of the urachus Boyce and Vest are of the opinion that trauma as the basis of the etiology is likely

Another interesting feature is that this patient did not have a waddling gait Some feel that the waddling gait is due to an unstable pelvis caused by the widening of the pubic symphysis Lanman states that the waddling gait is caused only in a small part by the bony separation of the pelvic girdle and is largely due to the irritation from the constant wetting which limits the childs activities This case tends to confirm this opinion

CONCLUSION

A mild form of embryonic maldevelopment resembling exstrophy of the bladder requiring relatively simple repair is presented. This case is interesting because of its unusual occurrence and its compatibility with fairly normal life.

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VESICAL ENDOMETRIOSIS

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The terms endometriosis, endometrioma, ectopic endometriosis, adenomyoma, adenomyosis, etc. refer to the presence of tissue with the aspect and function of the uterine endometrium in a situation different from its normal one.

The condition is most frequently localized in ovaries, fallopian tubes, broad and round ligaments, cervix, vaginal wall, peritoneum and Douglas "cul de sac" with invasion of the rectum.

The invasion of the urinary tract by endometriosis is not very common, but it occurs with sufficient frequency for us to be interested in its clinical characteristics and its treatment.

Starr Judd in 1921 described the first case of vesical endometriosis in the literature. Up to 1945 a total of 64 cases had been reported, which number compared with the number of cases of endometriosis of other locations gives us a rate of incidence relatively low. As to age, the youngest reported case was 18 years old and the oldest 48. As Reynolds has established, vesical endometriosis depends on ovarian function and as a consequence it will only occur between the first menstruation and the menopause without any other incidence at any intermediate age.

Several theories try to explain the origin of endometriosis. The embryogenic theory of von Recklinghausen (1896) assumes the inclusion in tissues of remnants of Wolff's duct. Kossman considers them as derived from remains of Muller's duct. For Cullen they would be proliferation from the normal endometrium which would develop and propagate through the uterine wall.

The metaplasic theory of Ivanoff (1898) establishes that all the epithelia of the female genital tract are derived from the coelomic mesothelium and as a result of chronic irritation, inflammation, surgical trauma, or hormonal stimuli, the peritoneal serosa can undergo metaplasia, changing the normal columnar epithelium, forming one of glandular type which resembles the endometrium in its morphology and function. Meyer suggests that in vesical endometriosis there may be in addition metaplasia of the bladder epithelium due to diverse stimuli or the combination of both factors, peritoneal and vesical metaplasia producing the so called coalition type.

For the migratory theory, endometriosis would be due to an ectopic localization of the normal uterine mucosa by invasion, implantation or metastasis through the uterine wall (Cullen), the fallopian tubes (Sampson) or through the blood or lymph channels (Sampson and Halban).

Bladder endometriosis has been classified as primary and secondary, the secondary occurring after surgical operations, trauma, etc. or when it is shown that the lesion is continuous with the uterus, ovaries, tubes, etc., and primary when there is no demonstrable connection.

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The symptomatology of vesical endometriosis is characterized by its relation to the menstrual cycle. The symptoms are hypogastric pain of variable intensity without characteristic radiation which occurs two or three days before the menstrual flow, continues during menstruation and lasting at times a few days afterward, disappearing generally in the intermenstrual period but occasionally the pain is permanent with exacerbations during menstruation.

Dysuria occurs in the same cyclic form as the pain and hematuria which may be macroscopic or microscopic, its intensity in proportion to the degree of invasion of the bladder, maintaining the cyclic characteristics of the menstrual flow, but may continue between menstruations and becoming more intense during menstruation.

Hematuria may not occur in some cases, but when it presents itself, accompanied by pain and dysuria, a possible diagnosis of endometriosis is justified by the symptoms alone which would be confirmed by cystoscopy and biopsy.

Cystoscopically, vesical endometriosis is most frequently located in the base of the bladder, bas fond, trigone and around the ureteral orifices, and less frequently at the apex of the bladder (fig. 1).

An area of hypertrophic tissue or tumor mass is found at times round or multilobular, not very large, which is usually covered by a normal mucosa. Characteristically one or several dark blue colored cysts are seen, which are translucent resembling a grape, due to their hematic contents. The tumor zone is surrounded by a small edematous area, and may show an area of cryptic formation described by the Germans as "pores".

If the cystoscopic appearance is followed throughout the menstrual cycle, during the premenstrual period progressive increase will be noted in the size of the lesion, and also in the number of bluish cysts that reach their maximum during actual menstruation which can also occur at the lesion, producing abundant bleeding which makes observation difficult; this bleeding diminishes in the postmenstrual period.

At the intermenstrual period an appreciable decrease in size of the tumor and the surrounding edema is noted, the bluish cyst changing to a reddish yellow color.

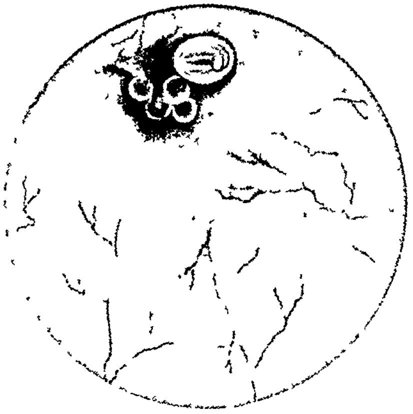

FIG. 1. Cystoscopic appearance of endometriosis of vertex of bladder represented by several violet colored vesicles. Rounded, more refringent zone corresponds to air bubble.

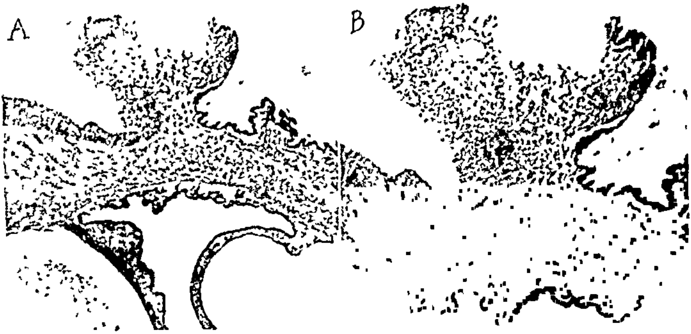

FIG. 2. *A*, low power view of vesical endometriosis. *B*, high power, clearly showing endometrial tissue.

Sections of the tissues are characteristic. We have described the macroscopic lesion in our comments on the cystoscopic appearance. Microscopic study of sections discloses the typical aspect of glandular endometrial tissue (fig. 2).

Treatment can not always be the same; it must vary according to the conditions present in each case. It can be directed in two fundamental manners: 1) to the supression of the hormonal stimuli and 2) the elimination of the endometrioma, depending on the age, location, extension of the lesions and the maternal desires of the patient.

Suppression of the hormonal stimuli can be obtained by surgical castration or by sterilizing doses of radiation. It is indicated in cases of intense symptoms, of location difficult for removal or when it occurs near the menopause; in this last instance, if the intensity of the symptoms permit it, we can wait for the physiologic suppression of the hormonal stimuli.

As to the removal of the endometrioma, open operation is the ideal treatment when the location permits it, especially in young women whose possible maternity we must respect. Electrocoagulation has been used, but most authorities consider it harmful.

RÉSUMÉ OF CLINICAL HISTORY

Department of Urology, University Hospital, No. 51,686, T. L. Z., aged 26 years, a half-breed, married woman stated that for an undetermined time after each menstruation she suffered from intense pain in the hypogastrium that occasionally made micturition difficult. Menstruation also was painful. For the last 5 years she had had pain in both lumbar regions. She had lost 10 pounds in 3 months. The family history was not contributory. For several occasions, during the past 2 years, she had been treated for an abundant vaginal discharge. She had had three normal pregnancies.

Examination disclosed an appendectomy scar, a second degree perineal tear, a uterus of normal size, position and consistence. A medium sized cystocele was found. An abundant vaginal discharge was present. Cystoscopic examination revealed good bladder capacity. At the vertex of the bladder, and to the right of the air bubble, a hypertrophied area was noted about 2 cm. in diameter, mammillary with violet colored areas, covered by mucosa and surrounded by a narrow zone of bullous edema. Because of the hardness of the lesion, it was impossible to take a biopsy. All laboratory data were within normal limits. A plain x-ray film was negative for calculi; a small spina bifida occulta of the first sacral vertebra was present. Excretory urography showed good function of both kidneys. Both renal pelves and ureters were normal.

Under general (endotracheal) anesthesia a median infra-umbilical incision was made exposing the bladder transperitoneally. Adhesions to the greater omentum were localized to the point of implantation of the urachus to the vertex of the bladder. After freeing the omentum, a partial cystectomy was done removing a fragment about 3 cm. in diameter from the vertex of the bladder. The bladder was closed in layers by interrupted sutures of No. 1 chromic gut. A dePezzer retention catheter was left in the urethra.

Convalescence was normal. The retention catheter was removed on the eighth postoperative day, and the patient was discharged 12 days after operation.

Pathological report (Dr. Fabiola Costales): In the center of the gross specimen a fragment of vesical mucosa was found, 3 cm. in diameter, and infiltration 2.5 cm. in diameter, which extended to the peritoneum. Microscopic examination revealed infiltration of the entire vesical wall by glandular endometrial tissue. At times the glands were dilated forming cysts with hematic contents. Young cellular stroma was present. Diagnosis: Endometriosis.

CONCLUSIONS

The different etio-pathological theories to explain vesical endometriosis have been reviewed, and the symptoms described.

A case of vesical endometriosis cured surgically has been reported.

117 Aguila St., Havana, Cuba

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OVARIAN DERMOID PRODUCING A HAIR GROWING BLADDER DIVERTICULUM: CASE REPORT

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Dermoid tumor of the ovary extending into the bladder is a relatively rare condition, but, as early as 1700, Wallace[1] observed that the symptoms of tumor, infection and pilimiction were characteristic of this disease. In 1909 Germain collected a series of 24 dermoid tumors, of which fifteen were well authenticated cases of ovarian dermoid extending to involve the urinary bladder.[2] In an earlier cursory treatise Clado discussed 32 cases of dermoid tumors which were near, attached to, or arising from the bladder or ovary, but he did not give detail enough in these cases to determine the origin of the pathological process.[3] Eighteen of the cases had a history of discharging dermoid material from the bladder and seven others had tumors arising in the ovary. He failed, however, to present a single case of ovarian dermoid extending to the bladder.

Since the original work of Germain, five separate and well documented cases have been presented by individual authors.[4, 5, 6, 7, 8] Six other cases reported after his thesis have been quoted as cases of ovarian dermoid extending into the bladder, but a review of these articles leaves considerable doubt about the origin of these tumors[9, 10, 11, 12, 13]

The following case from the University of Virginia is presented:

M. T., 206680, a 49 year old Negress, was first admitted to the hospital in October 1944, following an incomplete abortion and was treated with dilation and curettage. At the time of admission, a catheterized specimen of urine showed eight to nine white blood cells per high power field, but this was not investigated further. The patient had no urinary symptoms in 1944.

She was next admitted to the hospital in June 1946 on the obstetrical service with a full term pregnancy, complicated by transverse presentation and placenta praevia. X-rays at this time revealed a 1½ cm. calcified mass in the interior of the bony pelvis At cesarean section, a mass measuring 5 by 6 by 3 cm was attached to the bladder This was identified as the right ovary and left undisturbed Five catheterized urines during this hospitalization revealed innumerable white blood cells. Treatment with sulfa drugs failed to eliminate the pyuria.

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In November 1946, the patient was seen in the Urology Department complaining of dysuria, occurring once each month, nocturia and daytime frequency. She was again treated with sulfadiazine but failed to return for further studies. The patient was again hospitalized in July 1949 complaining of a recurrent mass in the right groin which would disappear on lying down. At surgery a hydrocele of the canal of Nuck was excised and a direct inguinal hernia was repaired. Urine analysis during this hospitalization revealed only an occasional white blood cell.

She returned to the Urology Department on September 2, 1952, complaining of recurrent nocturia and burning upon urination. Centrifuged urine analysis had twenty to thirty white blood cells per high power field and the patient was treated with gantrisin. When she returned on September 18, the pyuria was still

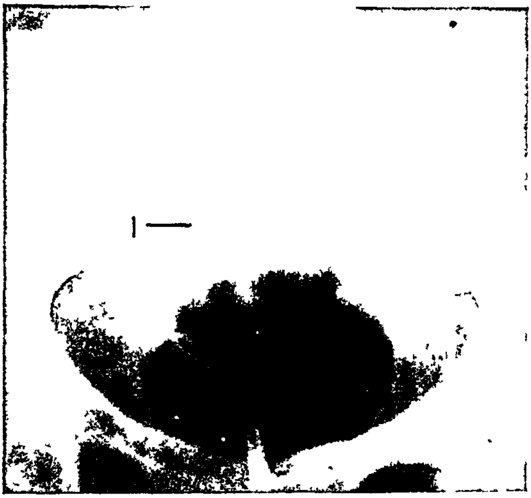

FIG. 1. Air cystogram showing proximity of ovarian dermoid to bladder.

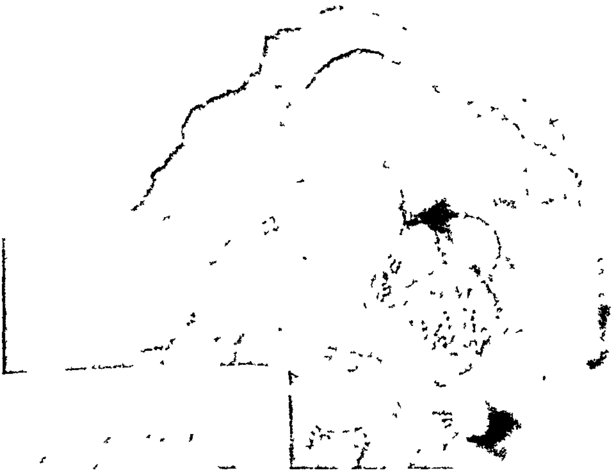

FIG. 2. Ovarian dermoid and cuff of bladder showing hair growing from bladder diverticulum.

present. Cystoscopy revealed a large solitary bladder calculus. Using trilene inhalation anesthesia an attempt was made to crush the stone with the Bigelow lithotrite but the anesthesia was inadequate and the procedure was discontinued.

One week later the patient returned for admission to the hospital and under pentothal anesthesia, the stone fragments were crushed more completely and removed transurethrally. As the stone was crushed it was noted that the center consisted of numerous pieces of hair. Further examination of the bladder revealed a diverticulum in the right side of the bladder dome. Several hairs were protruding from this diverticulum. The following day a cystogram with sodium iodide demonstrated the diverticulum and the same calcified mass which was seen in the x-rays of 1946. An air cystogram showed the proximity of the bladder diverticulum to the calcified mass (fig. 1).

Operation, September 20, 1952: A midline incision was made and the right ovary was identified as enlarged and adherent to the dome of the bladder. An elliptical incision was made in the bladder and the right ovary and adherent segment of bladder were excised as a single specimen. The bladder was closed around a cystostomy tube and a urethral catheter was inserted.

Postoperative course was uneventful and the patient was discharged from the hospital on the ninth postoperative day, her wound healed, voiding well and with no complaints.

Pathology report (J. F. A. McManus, M.D.): The gross specimen consisted of a purplish, curled tube measuring 4.5 by 1.2 cm. which was attached to an ovary measuring 4.5 by 2.8 cm. There was some cystic change in the ovary, one of which appeared to have ruptured. Attached to one edge of the ovary was some mucous membrane. Some hair was growing from the ovary through the base of the mucous membrane. On sectioning the specimen, the peripheral portion of the ovary was swollen and contained fatty tissue and a structure which resembled a tooth. This measured 1.7 by 0.8 cm.

Microscopic: Portions of normal ovarian stroma were mixed with fibrous tissue and fat, external to the bladder muscularis. The bladder mucosa was covered by stratified squamous epithelium which was adjacent to a complicated dermoid cyst structure in the wall of which there were hair follicles and associated glands, as well as several glands which seemed to be salivary in type. Another section of the ovary showed nervous tissue.

Diagnosis: Ovarian dermoid extending into adherent bladder.

Follow up: The patient has remained in good health since operation. Urinalysis on October 13, 1952 revealed an occasional white blood cell and five to six red blood cells per high power field of centrifuged urine. She was last seen in February 1953 at which time the urine was negative and the patient free of urinary symptoms.

SUMMARY

The twenty-first case of ovarian dermoid extending into the bladder is reported. Unusual features of this case were a solitary bladder calculus containing hair and the cystoscopic observation of hair growing from a bladder diverticulum.

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VESICORECTOSTOMY THROUGH ITS FIRST FIVE YEARS

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Deviation of the urinary flow by nephrostomy, ureterostomy, cystostomy, ureterosigmoidostomy, and urethrostomy have had, and still have important roles in Urology as we find it today. The literature has frequently listed and described in detail the operations designed for anastomosis of the urinary and intestinal tracts. Among the men responsible for the progress in this field are Maydl, Bergenhem, Peters, Diakonow, Tizzoni and Foggi, Simon, Coffey, Verhoogen, Higgins, Shaw, Trendelenburg, Foley, Bisgard, Rubin and Wolff. To give an account of their ingenious methods and results would be unnecessary repetition.

This paper is the result of a search for a satisfactory method of urinary deviation which would overcome the undesirable factors of previous operations. The distasteful effects of cutaneous nephrostomy, cystostomy, and cutaneous urethrostomy are well known. Specifically, ureterosigmoidostomy deserves reconsideration since few will deny that this procedure carries late systemic results, which shorten the patient's life by many years. One young patient with complete incontinence said that he had no particular interest in living to an old age, and that he would prefer to have a shorter but dry life. Such a decision by a patient should be important in planning surgical management. If ureterosigmoidostomy would not initiate and maintain other detrimental alterations in human physiology the correction of anatomic defects would prove as simple to the surgeon as it was to this patient.

Unfortunately the dry life so desperately desired brings with it multiple systemic disturbances, which in practically all cases sooner or later profoundly detract from the patient's physical comfort. The physiologic changes are the sequelae of various mechanisms. The most harassing of these is obstruction at the site of the anastomosis. Early this is manifested by the chills, fever, pain and, at times, septicemia of acute pyelonephritis. Frequently bilateral hydro-ureter and hydronephrosis can be demonstrated. Upper urinary calculi are common when these conditions prevail. Another mechanism is colonic re-absorption which will begin shortly after ureterosigmoidostomy when the ureters are inserted proximal to the rectosigmoid juncture where, according to Gaston, there is a competent sphincteric action. The resulting hyperchloremic acidosis which occurs in about 80 per cent of the cases is not difficult to control and it is frequently asymptomatic. If these patients do not die of a recurrence of the original carcinoma, or of some other unrelated cause, they almost invariably go on to uremia, which gradually becomes more severe with its nausea and vomiting. This distressing stage may be prolonged for many months or years. When this hyperchloremic acidosis is severe

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or prolonged, there is an added tendency to the development of a generalized osteomalacia This occasionally becomes so painful that the patient is continuously confined to bed

I have enumerated these effects because there have been several papers written which have as the chief object, an estimation of how long these patients will live, but I have seen none which dwells on how they live concerning a comfortable existence

One of the purposes of this paper is to present a plea for continued efforts to develop methods that will prevent ureteral obstruction and to minimize re-absorption of urinary components by the colon in cases where we find it necessary to delegate the work of the urinary sphincters to the anal sphincters

A second purpose is to point out that these aims have been accomplished and are still maintained at the present date, which amounts to a period of more than five years

DESCRIPTION OF OPERATION

The first patient on whom this operation was performed had complete epispadias, with urinary incontinence, all of his twenty-two years of life The first stage of the operation was carried out through a midline suprapubic incision The bladder was exposed and opened with a vertical incision Two fingers of the left hand were inserted into the bladder and pressed on its posterior wall as two fingers in the rectum pressed forward and afforded excellent bimanual palpation It was readily ascertained that no omentum or other intraperitoneal structure was low in the rectovesical pouch A fairly large area was felt where the anterior wall of the rectum came into apposition with the posterior wall of the bladder It was the center of this area that was selected for the anastomosis of the two organs The future stoma was visualized as oval in shape, extending from the posterior bladder wall to a distance of one centimeter on the trigone (fig 1) The lateral edges of this oval would be about ½ cm medial to the medial edge of each ureteral orifice Sutures were then placed in the shape of a horseshoe with the open portion on the trigone These were interrupted sutures of 0 chromic catgut An assistant, wearing a metal thimble on his index finger, was able to push both walls upward The threaded needle was then passed through the bladder wall first, and then through the rectal wall until the metal thimble could be felt with the point of the needle The needle was then reversed and emerged in the lumen of the bladder

The sutures were placed about ⅛ cm apart and continued until the horseshoe was completed Sutures were not placed in the open portion on the trigone because of the remote possibility of tying off the blood supply and producing necrosis within the oval before the two walls had firmly healed together The next step was probably unnecessary but since there was no precedent for reference, extra precaution was taken to guard against urinary infiltration into the space between the serosa of the bladder and the serosa of the rectum Into this space and into the rectal and bladder walls a sclerosing solution was injected at numerous points throughout the oval area The urethra was then closed just distal to the verumon-

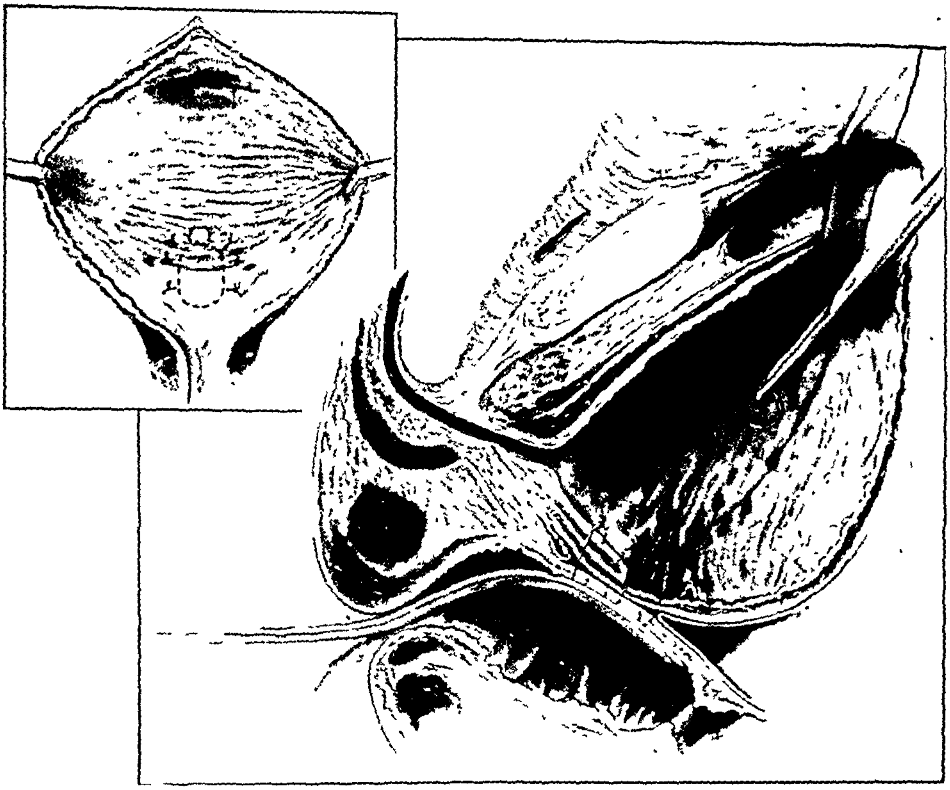

FIG. 1. First stage of vesicorectostomy

tanum by the mucosa to mucosa and skin edge to skin edge. A mushroom catheter was placed in the bladder so that it emerged from the upper angle of the incision. The bladder was then loosely closed around the catheter and the incision was sutured in layers. Two weeks after the first stage the patient had the second stage of the operation. After opening the bladder again a section just within the suture line between the ureteral orifices was excised. The ostium was about 40F. The anastomosis was re-inforced by several interrupted sutures around the circumference. A long curved clamp was then passed from the bladder through the ostium and anus to grasp a 38F rubber tube with a beveled end (fig. 2). This was drawn into the bladder and held securely there by a silk suture, which was anchored to the skin on the left side of the suprapubic incision. The bladder incision was then closed tightly and the fascia, muscle, and skin edges were approximated. After 2½ weeks the rubber tube became obstructed with calcareous deposits and it was removed.

In the second case the operation was completed in one stage because there had been a chronic inflammatory reaction about the urethra and bladder for many years. It was decided that this patient had sufficient fixation of the anterior rectal wall to the trigone and floor of the bladder. This allowed the omission of the preliminary suturing, injection of the sclerosing solution, and the two weeks of waiting for attachment of the two organs. After removing the suprapubic tube the bladder was exposed and the fistulous opening was enlarged by a vertical

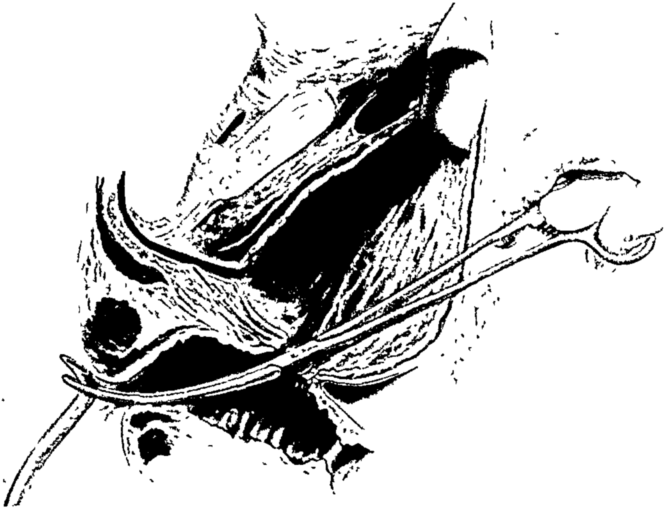

FIG. 2. Second stage of vesicorectostomy

incision. As in case 1, an oval section was removed by sharp dissection. It consisted of bladder and rectal walls, including bladder mucosa and rectal mucosa. The blade of the scalpel cut from the lumen of the bladder to the metal thimble in the rectum. The ureteral orifices were clearly visible and were carefully avoided as the section was excised between these orifices and included part of the trigone. The interrupted sutures of chronic catgut around the circumference of the newly formed ostium were passed from rectal mucosa to bladder mucosa. After taking the rubber tube through the anal canal, rectum, and into the bladder it was fixed there by a silk suture as in the first case. The bladder and suprapubic incisions were then firmly closed. Before leaving the operating room urine was seen coming through the tube which emerged from the anal canal.

CASE REPORTS

Case 1. A man, 20 years of age, L. R., Presbyterian Hospital, University of Pittsburgh Medical Center, had complete epispadias with urinary incontinence since birth. His mother gave the history that in infancy he had two operations for correction of the epispadias without success. I first saw him in June 1946, and in that month performed the operation described by Dr. Hugh Young, which consisted of excising a portion of the anterior wall of the bladder and posterior urethra. This produced some constriction of the urethra, bladder neck and funneling portion of the bladder. Following the operation he continued to have incontinence. Believing that further constriction was necessary the same operation was repeated in February 3, 1947. After this operation he was able to retain about three ounces of urine for short intervals but after about one month he was again completely incontinent. Many types of collecting apparatus were tried but none were satisfactory. His bladder was very intolerant of indwelling catheters which were promptly expelled.

On June 16, 1948 he entered the Presbyterian Hospital and preparation was started for an anticipated bilateral ureterosigmoidostomy, which was then accepted as the customary procedure for a patient in his situation. His blood nonprotein nitrogen and other laboratory studies were normal and excretory urograms showed a normal upper urinary tract (fig. 3, *A*). After deliberation the original plan of operation was changed and on June 28, 1948, he had the first stage as described, and 14 days later on July 12, 1948, he had the second stage. After each stage there was very little discomfort and practically no fever. The tube drained urine well for 2½ weeks and then became occluded and had to be removed. From then he passed urine from the rectum satisfactorily, and left the hospital 8 days after the tube was removed. Three weeks after leaving the hospital he complained of a sense of fullness in the bladder. The ostium was found constricted and it was dilated up to 38F. Five weeks after the dilatation he again required dilatation. On this occasion a rubber button was made by telescoping the bulbous ends of two de Pezzer catheters. After sewing them together one bulb was placed in the bladder and the other in the rectum. This was kept in place for 2 weeks for prolonged dilatation. Since that time he has never required dilatation of the ostium. This patient is a school teacher and has continued with his work without loss of time for the last 5 years. During this time he has had two complications. One was mild epididymitis which responded to medication. The other was the formation of two stones in his posterior urethra which is similar to a small diverticulum of the bladder. The stones were easily removed and have not recurred. These complications could have been prevented by closing the internal urethral meatus. On August, 1953 his blood nonprotein nitrogen was 37; plasma CO_2, 20 m/Eq; chlorides, 103.1 m/Eq; Na, 145 m/Eq; K, 4.5 m/Eq; Ca, 11 mg.; and phosphates, 4.5. Hemoglobin, 100 per cent; red blood cells, 5,360,000; white blood cells, 7,450.

August 1953, cystoscopy revealed normal bladder mucosa. With the retrograde telescope the ureteral orifices appeared normal. On August 13, 1953, excretory urograms showed a normal upper urinary tract which appeared the same as it did about 5 years ago before operation. See figure 3, *B*, *C*, *D*.

Case 2. W. T., 56 years of age, Presbyterian Hospital, University of Pittsburgh Medical Center, was admitted complaining of urethral strictures and multiple fistulas to the scrotum, penis, and perineum. He gave a history of repeated abscesses at the sites of the fistulas. He had required a suprapubic cystostomy for 11 years. Examination revealed impassable urethral stricture and a markedly contracted bladder. The scrotum, perineum, and penis were swollen, indurated and tender. The laboratory findings were normal. The excretory urograms showed poor visualization of each kidney and tortuous, dilated ureters. On November 9, 1951, he had vesicorectostomy as described above. He had no febrile reaction and no postoperative pain. A tube was kept in the ostium for 3 weeks. The suprapubic incision healed promptly. Six weeks after leaving the hospital the ostium was palpated. The bladder felt normal and the ostium did not require dilatation.

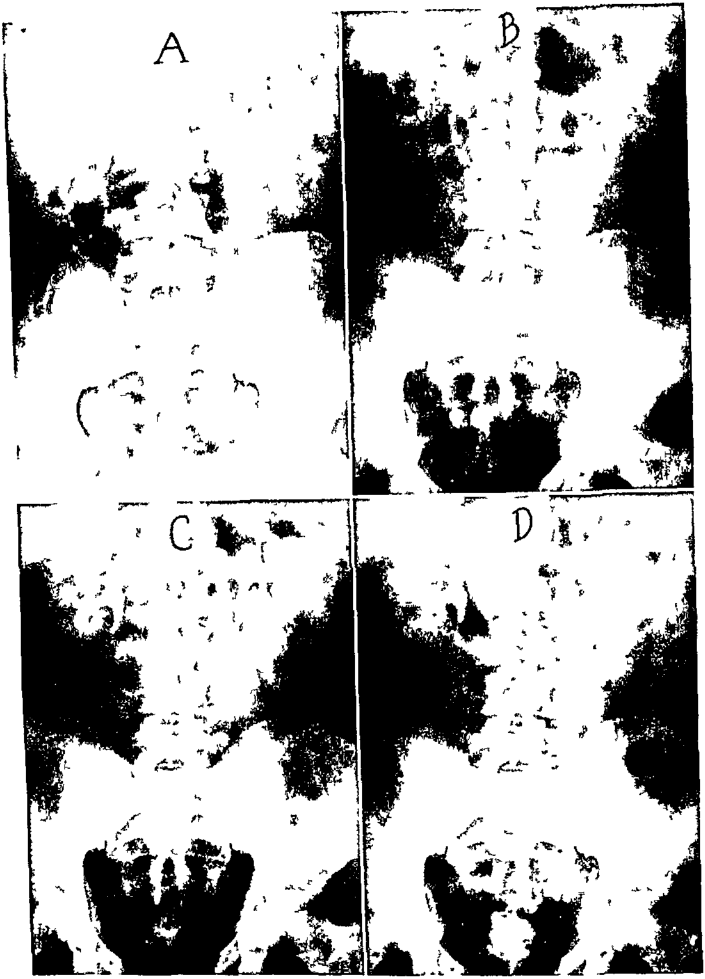

FIG 3 Case 1 *A*, excretory urogram before operation *B*, plain x ray 5 years after operation *C* excretory urogram 5 years after operation No change from *A* *D*, excretory urogram 5 years after operating showing diodrast in rectum and normal lower ureter on each side

On September 9, 1953 he reported that he had a normal bowel movement in the morning and passed clear urine from the rectum about every three hours during the day The swelling and tenderness of the scrotum and perineum had entirely subsided There was no passage of urine through the urethra or fistulous tracts

This patient feels so well that I have been unable to persuade him to enter the hospital for laboratory and x-ray studies.

INDICATIONS

Vesicorectostomy is indicated for 1) urinary incontinence when urethral operations are inadequate and where the anal sphincters are competent; 2) urethral carcinoma; 3) some cases of urethral stricture; 4) exstrophy of the bladder, 5) severe Hunner's ulcer when it does not respond to other therapy; 6) the contracted bladder of healed tuberculosis; 7) more radical prostatectomy.

DISCUSSION

Since case 1 was the first patient ever to have the operation of vesicorectostomy I deferred general recommendation of the procedure until all the results over a period of 5 years were known. Now that clinical, laboratory and urographic reports show such good effects I hope that the operation will be more widely used. Why should there be such a departure from the standard surgical procedures? In this instance it was the reluctance to relieve the incontinence at the risk of submitting him to the probable, immediate and late complications of ureterosigmoidostomy that prompted me to review the anatomic proximity of the bladder and rectum. The importance of the interdeferent triangle then became apparent because it is over this triangle that normally the bladder and rectum are in direct apposition. This is the triangle bounded by each vas deferens and by the lower border of the rectovesical or rectogenital pouch. However, these organs are still separated by the so called fascia of Denonvilliers or what Uhlenhuth et al. called the rectogenital septum, which is not a fascia but is of peritoneal origin representing the fusion of the dorsal and ventral walls of the rectogenital pouch. Uhlenhuth et al. in that study also learned that the rectogenital pouch remained lower in infants than in adults. This indicates that the interdefferent triangle is relatively and actually larger in adults than in infants which means that there is a better margin of safety for adults having vesicorectostomy. A patient of Dr. Richard A. Gill was seen with congenital absence of the urethra and imperforate anus. On July 15, 1952, this infant had vesicorectostomy. In about three months the bladder again became distended. The ostium was contracted, but patent. It was enlarged and functioned again for several months but then the bladder again became distended. Dr. Gill informed me that then he performed bilateral ureterosigmoidostomy. Drs. Boyce and Vest reported similar operations on two patients with exstrophy of the bladder. Their first case was operated on August 15, 1950. Ten days before this the patient had a colostomy and a rectosigmoid pouch was constructed for the purpose of acting as a urinary reservoir. Ten months after operation a normal upper urinary tract was found. Their second case was treated in the same manner and equally good results were obtained. The cases presented in this paper confirm the opinion of Dr. E. A. Gaston in his paper, "The Physiology of Fecal Continence," in which he stated that there was a plastic adaption of the sigmoid to the enlarging fecal mass and in the normal adult it is evident in the practically constant finding, by x-ray and sigmoidoscopy, of fecal material collected in the sigmoid above an empty rectum, without the aid of a demonstrable sphincter. Both of these patients report that except on a few occasions, they have a normal bowel movement in the morning and during the rest of the day pass clear urine from the rectum. This complete segregation of urine and fecal material shows how the rectum, which usually lies inactive most of the day, will, in its spare time, willingly function as a urinary bladder.

SUMMARY

A widespread opinion exists in the medical profession that we should become resigned to accepting the morbidity of ureterosigmoidostomy, and probably for this reason the severity of this morbidity does not seem to be sufficiently appreciated by the profession or by the general public. Such an attitude is conducive to complacency in combating the complications of intestinal urinary deviation selected by these patients who were anxious to escape the inconveniences and offensive aspects of cutaneous urinary drainage. The operation presented eliminates most of these complications because the ureters are never involved in any part of the procedure. They are not incised and the distal terminals retain the same oblique transvesical positions with their natural valve action. Furthermore, there is no injury of the mucosa and no interference with the nerve or blood supply of any part of the ureters or ureteral orifices. The preservation of the complete, original anatomy of the ureter should exclude cicatrization and angulation and thus afford indefinite assurance against ureteral obstruction. The less important complication is intestinal re-absorption with its accompanying hyperchloremic acidosis. Following the operation described one would expect the least amount of re-absorption due to the fact that the reservoir is formed by the most distal portion of the alimentary canal. This impression is confirmed by the case of the first patient, who has functioned with vesicorectostomy longer than anyone. After 5 years he had no symptoms or physical signs of hyperchloremic acidosis and no x-ray evidence of osteomalacia. His laboratory reports on plasma chlorides, plasma carbon dioxide, plasma bicarbonate, sodium, potassium, calcium and phosphorus were normal. The second patient, almost two years after operation, had no symptoms or physical signs of acidosis. He did not report for laboratory studies. Both patients volunteered the information that there was complete segregation of urine and feces, except for rare occasions. In each case defecation occurred in the morning and clear urine was expelled during the day. The first patient retains urine for as long as 7½ hours and the second for as long as 3 hours.

CONCLUSION

A new method of urinary deviation is described and illustrated. This method was designed to prevent ureteral obstruction and decrease intestinal re-absorption. By means of this operation the anal sphincters have been utilized to regulate the voluntary expulsion of clear urine. A 5-year postoperative observation period revealed no evidence of dilatation or infection of the upper urinary tract, and no signs of re-absorption by the intestines. I now believe that this operation can be recommended for various conditions which are listed.

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TRANSURETHRAL VESICAL NECK RESECTION, AN A
THE MANAGEMENT OF THE NEUROGENIC BLA

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The aim of the physician who takes care of spinal cord injuries has been to eliminate eventually intra-urethral, suprapubic or perineal catheters The neuro urological problem is quite different from that encountered in general Urology where a transurethral resection for obstructive uropathy is performed and which usually yields prompt and good results

The treatment of our cases with cord bladders is started with tidal drainage, Munro's bladder training and pudendal blocks when indicated before any surgery is attempted During the conservative period of treatment many obstacles may arise that prolong therapy such as penoscrotal fistulas, vesico-ureteral reflux, pyelonephritis, calculosis of the kidney, ureter and bladder and also non-urological complications such as severe decubiti and spasticity The mental attitude of the patients is of importance This conservative period may last from several weeks or months to nearly a year If conservative measures fail then operative procedures must be considered such as transurethral resection, pudendal nerve operations, sacral nerve operations, anterior and/or posterior rhizotomies, subarachnoid injections with absolute alcohol and presacral neurectomies

All patients during the conservative period should have an excretory urogram, cystoscopy, cystometry, sphincterometry, cystograms, urethrograms, as well as frequent checks of the bulbocavernosus reflex, rectal tone and anal cutaneous reflex During the period of spinal shock the findings of all bladders resemble those of a lower motor neuron type bladder, therefore, before pudendal blocks are performed this phase of shock must have disappeared and the findings compatible with an upper motor neuron type bladder must be present The level of the lesion *per se* is not necessarily decisive as to the type of the bladder, e g , a high thoracic lesion does not always lead to an upper motor neuron type bladder but may, owing to descending degenerations from thrombosis of the spinal vessels, become a lower motor neuron lesion with the characteristic type bladder

This author agrees with Emmett who stated that "the surgeon who takes it on himself to care for patients who have cord bladders must possess considerable patience and optimism "

CLASSIFICATION OF NEUROGENIC BLADDERS

Abundant references have been quoted on the physiological concepts of micturition, although this seems to have escaped the attention of some Despite the similarity of experience with the urological treatment of paraplegic patients, many authors complained about the lack of a satisfactory classification of the neurogenic vesical dysfunction If one accepts as the cause of disturbance an im

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balance between the expulsive (detrusor) forces and the retaining (vesical neck, external sphincter and pelvic floor) forces of the bladder, a rational treatment cannot be based on an exclusively mechanical attitude illustrated by the statement "that it makes very little difference what part the sympathetics, parasympathetics and somatic nerves play in the act of urination."

Among the existing variety of classifications we used that advocated by Bors, who based it upon known neurophysiologic facts and accepted neurologic nomenclature in conjunction with urologic terminology of bladder function, expressed by the ratio of residual to capacity.

This classification, in brief review, depends essentially on whether the lesion in the spinal cord is above the conus medullaris (the spinal integrating center for micturition) or whether the lesion is in or below the conus medullaris, i.e. the cauda equina, or both. If the conus is undamaged, the reflex patterns are intact; this type of bladder accompanies an upper motor neuron lesion of the striated muscles of the pelvic floor. If the lesion is in the conus or cauda equina, the reflex patterns are disturbed and this type accompanies a lower motor neuron lesion of the pelvic floor. Each major class has been further divided according to the extent of the cord damage into a complete or incomplete lesion. And finally the term of bladder function is introduced as balanced or imbalanced with regard to the residual/capacity relationship. All cases treated on our service are therefore classified as having upper or lower motor neuron types of neurogenic bladders, and the treatment depends on the type. As has been mentioned before, in all patients tidal drainage and bladder training are used initially. However, even during the early conservative therapy, pudendal blocks are used in upper motor neuron types of bladders. When conservatism fails surgery is considered. The surgery indicated in a lower motor neuron type is transurethral resection. Surgery in the upper motor neuron type could consist, depending on the circumstances, of the following procedures or their combinations: transurethral resection, pudendal neurotomy, sacral neurotomy, rhizotomy, subarachnoid alcohol blocks or presacral neurectomy.

The purpose of this paper is to present the results of the transurethral resections performed on our service from April 1, 1946 to April 1, 1953.

STATISTICS

Table 1 reveals that 151 patients had 228 resections. One hundred and thirty-nine patients had traumatic lesions and 12 had nontraumatic lesions caused by disease or tumor. Ninety-four (62 per cent) of the patients (87 traumatic and 7 nontraumatic) had one transurethral resection. Forty-two (28 per cent) of the patients (38 traumatic and 4 nontraumatic) had two transurethral resections. Eleven (7 per cent) of the patients (10 traumatic and 1 nontraumatic) had 3 transurethral resections. Three (2 per cent) traumatic patients had 4 transurethral resections. One (1 per cent) traumatic patient had 5 transurethral resections (table 1).

During this period of 7 years 905 patients were seen. Seventeen per cent of all the patients had a transurethral resection.

TABLE 1

Number of Transurethral Resections	Number of Traumatic Patients	Number of Nontraumatic Patients	Total Number of Patients	Percentage of Patients	Total Number of Transurethral Resections
1	87	7	94	62%	94
2	38	4	42	28%	84
3	10	1	11	7%	33
4	3		3	2%	12
5	1		1	1%	5
	139	12	151	100%	228

Results of T U R with or without combinations

	UMN*		LMN*		Alcohol*			Pudendal*		Dis Tum *	
	Good	Poor	Good	Poor	Good	Fair	Poor	Good	Poor	Good	Poor
1 Transurethral resection	44	5	19	2	8	1	1	7	0	6	1
2 Transurethral resections	22	1	7	0	4	0	0	3	1	4	0
3 Transurethral resections	3	1	1	0	0	0	1	2	2	0	1
4 Transurethral resections	2	0	1	0	0	0	0	0	0	0	0
5 Transurethral resections	0	1	0	0	0	0	0	0	0	0	0
Total no of patients—151	71	8	28	2	12	1	2	12	3	10	2

* Symbols

UMN—Upper Motor Neuron Type of Bladders with T U R only

LMN—Lower Motor Neuron Type of Bladders with T U R only

Alcohol—UMN Bladders converted to LMN Bladders by subarachnoid alcohol block with additional T U R

Pudendal—UMN Bladders with pudendal neurotomy and T U R

Dis Tum —*Nontraumatic Spinal Cord Lesions (Disease or Tumor)* with T U R and additional procedures

Among the 94 patients with one transurethral resection the following observations were made 44 cases with upper motor neuron type bladders had a good result without additional procedures, whereas 5 had a poor result Nineteen patients with lower motor neuron type bladders had good results, whereas 2 had poor results Ten patients with upper motor neuron type bladders had subarachnoid alcohol blocks because of spasticity of the lower limbs and abdomen Two of the 10 patients had had transurethral resections before the injection with good results, the bladder balance remained good after the alcohol block Seven of the 10 patients, after having the alcohol block had good bladder balance immediately but later required one transurethral resection, the time interval between subarachnoid alcohol block and transurethral resection in the 7 cases was 10, 26, 26, 34, 38, 67, and 74 months respectively Following the transurethral resection, two of the 7 cases had a poor and fair result respectively, 1 of the 10 patients did not attain good immediate balance from the alcohol block and required a transurethral resection 6 weeks later with good results Seven patients with an upper motor neuron type of bladder were submitted to a pudendal *neurotripsy* or neurotomy, with good results. Three of the 7 patients had a pudendal operation before the transurethral resection, 3, 4, and 12 months respectively. The results were equivocal. A transurethral resection afterwards ended in good bladder balance in all 3 cases. Four of the 7 patients had poor to fair results following a transurethral resection, and pudendal operations were performed with good results in these 4 cases, 1, 4½, 5, and 13 months respectively after the transurethral resection. Seven patients had nontraumatic lesions of which 6 had good results and 1 had a poor result following transurethral resection.

Among the 42 patients with two transurethral resections were: 22 cases with upper motor neuron type bladders that had a good result without additional procedures, whereas 1 had a poor result. Seven patients with lower motor neuron type bladders had a good result. Four patients with subarachnoid alcohol block had transurethral resections 2, 2, 11, and 18 months respectively after the block, with good results. Four patients were subjected to pudendal operations. One of the 4 had a good result from a transurethral resection, but his bladder became imbalanced 17 months later requiring a pudendal operation; again the bladder went into a gradual imbalance requiring a transurethral resection 21 months after the pudendal operation, with a good result. One of the four had 2 transurethral resections 11 months apart, and 5 weeks after the second transurethral resection a pudendal operation was performed with a good result. One of the 4 (a quadriplegic) had a transurethral resection with short lived good results. This was followed shortly by a bilateral pudendal neurotomy with poor results and finally responded well, 2 months later, to a transurethral resection. One patient had 2 transurethral resections followed by a bilateral pudendal operation with a poor result.

Among the 11 patients with 3 transurethral resections were: 3 cases with upper motor neuron type bladders which had a good result without additional procedures, whereas 1 had a poor result. One patient with a lower motor neuron type bladder had a good result with additional procedures. One patient had an alcohol block followed by 3 transurethral resections with a poor result. Four patients were subjected to pudendal operations. One patient had 2 transurethral resections followed by a bilateral pudendal operation with a good result following a third transurethral resection after the pudendal operation. One patient had 3 transurethral resections followed by a pudendal operation, with a good result. One patient had 3 transurethral resections followed by a pudendal operation, with a good result, but 3 months later went into imbalance because of regeneration of the pudendal operation, with a poor result. One patient with a nontraumatic lesion had 3 transurethral resections with a poor result.

Three patients had 4 transurethral resections: two of them with upper motor neuron type bladders had a good result without additional procedures; 1 case with a lower motor neuron type without additional procedures.

One patient had 5 transurethral resections with a poor result.

The over-all results of the 151 patients including the nontraumatic group who had transurethral resections with and without additional procedures reveal that 133 (88 per cent) had good results; 1 (1 per cent) had a fair result; 17 (11 per cent) had poor results.

TABLE 2

Number of Transurethral Resections	Extremes of Total Tissue Removed in Grams	Average Weight in Grams
1	0.2-5.2	1.78
2	1.3-6.6	3.33
3	1.9-7.5	4.1
4	Not weighed	Not weighed
5	Not weighed	Not weighed

This table indicates the amount of tissue that was removed with one or more transurethral resections.

The over-all results of the 139 patients with traumatic cord lesions who had transurethral resections with and without additional procedures reveal that 123 (88 per cent) had a good result; 1 (1 per cent) had a fair result, and 15 (11 per cent) had a poor result.

The results of the 109 patients with traumatic cord lesions with *only* transurethral resections reveal that 99 (91 per cent) had good results and 10 (9 per cent) had poor results.

The results of the 79 patients with traumatic cord lesions with upper motor neuron type bladders and only transurethral resections reveal that 71 (90 per cent) had good results and 8 (10 per cent) had poor results.

The results of the 30 patients with traumatic cord lesions with lower motor neuron type bladders and only transurethral resections reveal that 28 (93 per cent) had good results and 2 (7 per cent) had poor results.

The results of the 15 patients with traumatic cord lesions whose upper motor neuron type bladders were converted into lower motor neuron type bladders by subarachnoid alcohol blocks and additional transurethral resections reveal that 12 (80 per cent) had good results, 1 (7 per cent) had a fair result and 2 (13 per cent) had a poor result.

The results of the 15 patients with traumatic cord lesions who had transurethral resections associated with pudendal operations reveal that 12 (80 per cent) had good results and 3 (20 per cent) had poor results.

The results of the 12 patients with nontraumatic lesions of the cord with transurethral resections reveal that 10 (83 per cent)—2 of which had pudendal operations, had good results and 2 (17 per cent)—1 of which had also an alcohol block, had poor results.

Table 2 shows the amount of tissue removed with one or more transurethral resections.

Table 3 illustrates how long after injury a transurethral resection was performed on the traumatic group *only* (139 patients), who had or had not additional procedures.

ANALYSIS OF POOR RESULTS

Out of the 151 patients who had transurethral resections with and without additional procedures, there were 17 poor results and 1 fair result.

There were 8 poor results in the group with upper motor neuron type bladders who had transurethral resections exclusively. One patient had one transurethral

TABLE 3

Months Since Injury	Number Of Patients	Months Since Injury	Number Of Patients	Months Since Injury	Number Of Patients	Months Since Injury	Number of Patients
4	1	21	3	42	2	67	1
5	4	22	2	44	2	68	1
6	5	23	3	48	2	73	1
7	3	24	1	49	2	74	1
8	7	25	3	50	2	76	1
9	7	26	1	51	1	77	2
10	5	28	1	52	1	78	1
11	4	29	1	53	1	79	2
12	5	30	2	54	1	80	1
13	2	31	3	55	2	82	1
14	3	33	1	57	1	90	1
15	2	35	2	58	2	93	1
16	1	36	2	60	3	97	1
17	2	38	3	61	2	100	1
18	2	39	2	62	1	101	1
19	1	40	1	63	1	127	1
20	2	41	2	66	4	240	1
						360	1

This table illustrates how long after injury a transurethral resection was performed on the traumatic group *only* (139 patients), who had or had not additional procedures.

resection. He declined to have another transurethral resection or any other procedure (e.g. pudendal operation) which might have helped. Another patient was discharged A.W.O.L. after the first transurethral resection. He, too, may have responded to further transurethral resections or pudendal operations. Three patients with one transurethral resection were tetraplegics. One underwent suprapubic cystostomy for nursing care; another had poor uninhibited detrusor waves; the third responded to sacral blocks temporarily. One patient with two transurethral resections did not return from leave so that further procedures were impossible. One patient with 3 transurethral resections refused further attempts at therapy. One patient had 5 transurethral resections; his bladder emptied reflexly from rectal stimulation. Since he is a tetraplegic he cannot perform this stimulation.

There were 2 poor results among patients with lower motor neuron type bladders who had transurethral resections only. All with repeated transurethral resections in this group responded with good results. The 2 poor results were in patients who had only one transurethral resection, and both refused an additional transurethral resection.

There were 2 patients in the group with subarachnoid alcohol block who had poor results. One had a fair result. The patient with the fair result preferred a suprapubic. One with a poor result had one transurethral resection and because a prefrontal lobotomy had to be performed for other reasons, he was left on catheter drainage. The other patient with a poor result had 3 transurethral resections and his poor response remained unexplained.

Three patients with pudendal operations had poor results; 2 of them had two resections. One with a T-2 lesion had abdominal spasticity which prevented Credé pressure, while at the same time his detrusor lacked strong uninhibited contractions. Following bilateral pudendal neurotripsy there appeared to be regeneration of nerve fibers as evidenced by the return of the bulbocavernosus reflex. Two patients had 3 transurethral resections associated with the pudendal operation. One had an excellent result following the pudendal operation, but regressed when, he too, developed signs of regeneration of nerve fibers. The other is a tetraplegic who has poor detrusor contractions on cystometry.

Two patients of the nontraumatic group had poor results. One of them refused further therapy after the first transurethral resection. The other has had 3 transurethral resections and an alcohol block.

DISCUSSION

The percentage of resections (17 per cent) performed at our station resembles closely the figures of other authors, although in some instances a much higher percentage was reported. The percentage of good results (88 per cent) from transurethral resections or additional procedures compares favorably with the experiences of others. Among the usual complications were noted: 3 cases of epididymitis among 228 resections; none of our patients was vasectomized. Two cases had marked hemorrhage, one required 22 fulgurations. Among patients with less severe hemorrhage there were yet a few who needed 2 to 3 fulgurations. Since the following management was instituted the rate of postoperative hemorrhage has decreased: following transurethral resection a two-way Foley bag catheter is introduced and a continuous bladder irrigation with saline is carried out. This is done until the urine is grossly free of blood. We were fortunate not to have had fatalities as reported in the literature.

Multiple resections are the method of choice. The average weight of the resected tissue from our cases (table 2) is smaller than that in the literature. In 2 cases in which only 0.2 gm. tissue were removed from the posterior vesical lip in lower motor neuron type bladders, it was sufficient to create a well balanced bladder by the so-called "tenotomy" effect. Five and two tenth grams was the largest weight of tissue removed in one sitting from a lower motor neuron type bladder with resultant incontinence. In the literature it is reported that up to 10 grams of tissue have been resected. The paraplegic prostate is usually small, not only because our patients are young but also because of their testicular atrophy and, therefore, small multiple resections seem to be the safest method.

Although resection has been recommended along the entire circumference of the vesical neck, the majority of the cases presented here underwent only resection of the posterior vesical lip from approximately 3 to 9 o'clock, strictly adhering to the resection of muscle rather than prostatic tissue. In those cases which do not respond to this method, the anterior vesical neck lip is attacked in which striated muscles have been found. In 6 cases with lower motor neuron type bladders which required repeated transurethral resections, a good balance was obtained by eventually confining the operation to the anterior lip. In each instance striated muscle could be demonstrated in the resected specimen. We have not attacked the external urethral sphincter as indicated in the literature.

We do not fully concur with the statement that following transurethral resection there is a definite decrease in the incidence of pyelonephritis. Irrespective of how a bladder becomes balanced, whether spontaneously or operatively, one cannot forecast the amount of renal damage caused by vesico-ureteral reflux, calculosis, or other factors. Any balanced cord bladder can regress from apparently trivial causes such as a simple "cold," any systemic disease, following major surgery, or becoming bedfast for whatever cause may change the patient's routine. In table 3 the length of the time interval is shown before regression set in, which requires surgery. One patient is tabulated whose upper motor neuron type bladder regressed only after 360 months. As can be also seen from table 3, only 5 transurethral resections were performed within the first 6 months after injury, a viewpoint which we share with other authors that one should not operate before 6 months or even a year or more after the injury.

We and others were unable to confirm the statement that following transurethral resection urinary cultures become negative.

Anesthesia was not necessary in most cases. Sodium pentothal was a very satisfactory anesthetic for patients with incomplete thoracic and lumbosacral lesions. However, in cases with cervical lesions we prefer as routine spinal anesthesia, in order to prevent the formidable paroxysmal hypertension due to bladder distention.

As has been previously mentioned, pudendal blocks are used also during the conservative management of upper motor neuron type bladders. Some observations are worth mentioning such as that poor balance following transurethral resection could be occasionally corrected with pudendal blocks, or that in some cases when pudendal blocks prior to transurethral resection failed, a good balance resulted from a pudendal block following the transurethral resection. One patient had a routine posterior vesical lip resection with a poor balance result. Pudendal blocks yielded good immediate but only temporary results. Inasmuch as it did appear contra-indicated to interfere with the patient's erections by pudendal neurotomy a resection of the anterior vesical neck lip was performed instead, with a resulting good bladder balance. Striated muscle fibers were demonstrated in the specimen. In yet another patient with an upper motor neuron type bladder, pudendal blocks had an excellent but only temporary effect. This case was ideally suited for the crucial test whether a myotomy of the anterior lip alone could produce a similar relaxing effect like a pudendal neurotomy; this was the case and again striated muscles were demonstrated in the resected tissue. Thus, the peripheral interruption of the reflex arc with destruction of afferent and efferent fibers at their origin and ending in the muscle tissue proper yields a permanent result, not dissimilar to that observed temporarily by local anesthesia of the vesical neck.

Among the 17 poor results of our series, 8 could be attributed to the mental attitude of these patients. A careful analysis of the 8 cases revealed that with either additional transurethral resections or pudendal operations, good bladder balance could have been obtained had we had the co-operation of these patients.

Another 2 poor results showed regeneration of fibers following neurotripsy. From the results of our other pudendal operations we might assume that had neurotomies been performed these 2 cases may have had good permanent results. Another 4 cases that had poor results were tetraplegics. These cases are a problem from the point of view of nursing care, abdominal spasticity preventing Credé, lack of strong uninhibited detrusor contractions in some cases, inability to use the hands for Credé, paroxysmal hypertension and/or a combination of these factors. Another tetraplegic patient since his fifth transurethral resection has developed a good reflex bladder that empties upon rectal stimulation. However, he is unable to perform the necessary stimulation. There remain 2 poor results that we are unable to explain; both of these cases have been bedfast most of the time due to complications such as decubiti, spasticity, penoscrotal fistulas. There remains, then, one patient with a fair result which followed a transurethral resection. The patient preferred a suprapubic catheter. However, another transurethral resection may have resulted in a balanced bladder.

CONCLUSIONS AND SUMMARY

The therapy of neurogenic bladders depends on a neurophysiological and not only a mechanical concept.

The choice of therapy is logically simplified if a classification based upon neurological and functional considerations (Bors) is applied.

The conservative first phase of therapy is alike in all cases whether they have upper or lower motor neuron lesions; any surgical intervention to correct bladder balance should be delayed until—at least—6 months after injury. During the conservative period pudendal blocks can be used in cases with upper motor neuron type bladders.

When conservative therapy fails the following choice of procedure is advocated: for cases with a lower motor type bladder, transurethral resection is the only correct method. In cases with an upper motor neuron type bladder, transurethral resection should be done first if the patient has erections rather than to interrupt the pudendal nerves, while in the absence of erection this order is reversed and a neurotomy should precede the transurethral resection. Should the transurethral resection (especially the anterior lip) fail in a case which has erections but should pudendal nerve anesthesia be still—though temporarily—effective, severance of the nerves is indicated. If after a subarachnoid alcohol injection a poor bladder balance results, transurethral resection is the method of choice as in any other case with a lower motor neuron lesion.

One hundred and fifty-one (17 per cent) of the 905 patients required a transurethral resection during a period of 7 years of observation.

One hundred and fifty-one (139 traumatic and 12 nontraumatic) patients had 228 resections with and without additional procedures. Eighty-eight per cent had good results, 1 per cent had fair results, and 11 per cent had poor results.

One hundred and thirty-nine patients with traumatic lesions had transurethral resections with and without additional procedures. Eighty-eight per cent had good results, 1 per cent had fair results and 11 per cent had poor results.

One hundred and nine patients with traumatic lesions underwent transurethral resections only. Ninety-one per cent had good results and 9 per cent had poor results.

Seventy-nine patients with traumatic lesions and upper motor neuron type bladders underwent transurethral resections only. Ninety per cent had good results and 10 per cent had poor results.

Thirty patients with traumatic lesions and lower motor neuron type bladders underwent transurethral resections only. Ninety-three per cent had good results and 7 per cent had poor results.

Fifteen patients with traumatic lesion and a combination of subarachnoid alcohol blocks with transurethral resections had 80 per cent good results, 7 per cent fair results, and 13 per cent poor results.

Fifteen patients with traumatic lesions who underwent transurethral resections and pudendal operations had 80 per cent good results and 20 per cent poor results.

Twelve patients with nontraumatic lesions had transurethral resections with and without additional procedures. Eighty-three per cent had good results and seventeen per cent had poor results.

The causes of failures are analyzed.

The results are discussed.

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MUCINOUS ADENOCARCINOMA OF THE URACHUS: REVIEW OF THE LITERATURE AND REPORT OF A CASE

FRED K. GARVEY AND WILLIAM E. NUNNERY

From the Department of Urology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

The first descriptions of mucin-secreting adenocarcinomas occurring in the bladder apex or supravesical region were recorded in the latter portion of the nineteenth century. Unfortunately, however, the accounts were vague and poorly documented, and one can only guess at the true nature of these tumors. In 1930 R. Campbell Begg published a comprehensive and critical survey of the existing literature on neoplasms of the urachus, paying especial attention to the mucin-producing type; this survey listed 18 published case reports of mucinous adenocarcinomas of the urachus.

After a careful study of the literature on the subject we have found 49 histologically proven cases reported to date, not including the present case.

EMBRYOLOGY AND ANATOMY OF THE URACHUS

The embryology and anatomy of the cloaca, bladder and urachus have been described in detail by Keibel and Mall and by Begg.

On the basis of careful gross and microscopic examinations of 70 random specimens, Begg described the urachus as a musculofibrous tube that varies in length from 3 to 10 cm., averaging 5 cm. (fig. 1). At its vesical termination its greatest diameter may reach 8 mm., while the apex is usually 1 to 2 mm. in diameter. The urachus is invested by a thin sheath of fine connective tissue which is surrounded by fine areolar tissue, probably derived from the fascia transversalis. The muscular component consists of interlocking bundles of unstriped muscle. Inside the smooth muscle sheath and resting upon it there is a layer of dense, fibrous connective tissue. The lumen is lined by poorly differentiated transitional cell epithelium, which varies in depth from place to place. In some areas it is only 2 to 4 cells deep, while in others the epithelium may entirely obliterate the lumen. Begg maintains that the epithelial cord of the urachus never undergoes obliteration, though he admits that the lumen may become impatent as the result of epithelial proliferation or inspissated masses of cellular debris. In 33.3 per cent of the specimens examined by Begg, the urachal lumen was continuous with the interior of the bladder; in the remaining cases the lumen stopped at about the level of the vesical submucosa.

Representative cross sections of the urachus, when viewed through the microscope, reveal irregular islets of increased epithelial activity. In some areas, the lining cells invade the subepithelial fibrous tissue and form cell nests, some of which eventually become cystic epithelial-lined spaces. This process is particularly characteristic of the region of the urachovesical junction, where, on occasion, these cell nests become quite numerous and form fibro-adenomas.

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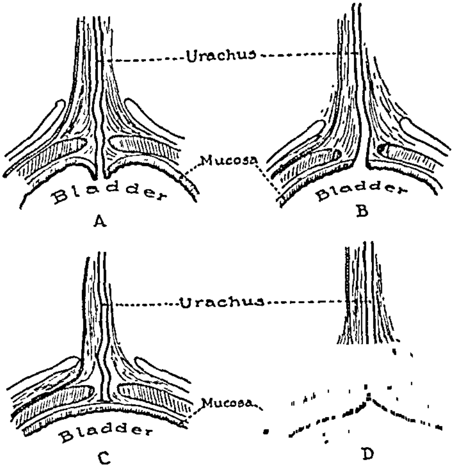

FIG. 1. Illustrative urachovesical insertions (from Begg)

THEORIES OF ETIOLOGY

Numerous theories explaining the presence of mucin-secreting goblet cells in these urachal tumors have been set forth and vigorously championed. None is satisfactory to explain the mucinous type of cells.

DIAGNOSIS

The symptoms depend to some extent on the location of the lesion—whether it is supravesical, intramural, or intramucosal, as first classified by Begg. As with other types of vesical neoplasms, silent hematuria is, by all odds, the commonest and often the only symptom. The patient, however, may also complain of a tender suprapubic mass, dysuria, frequency, and pyruia—usually in that order of occurrence. In rare instances, masses of gelatinous mucin have been noted in the urine by the patient. In slightly more than 20 per cent of the collected cases, a tender suprapubic mass was found on physical examination, and in about half of these cases it was the only symptom. A purely supravesical tumor may first manifest itself in this way, and may invade the bladder rather late in the course of the disease.

Direct visualization of the tumor through the cystoscope is possible except in those instances where the tumor is limited to the closed interior of a urachus that does not communicate with the bladder. Even in these cases indentation of the bladder dome is usually evident, suggesting pressure from without. The lesion, when visible, is usually described as a low, flat, clearly demarcated, reddish purple mass with an irregularly bosselated surface. This classic appearance, we feel, is probably encountered but rarely. Far more often, a ragged, poorly outlined papillary mass of friable pink tissue is found. The periphery may merge imperceptibly into edematous and hemorrhagic bladder epithelium. Some lesions appear only as areas of ulceration covered by a greyish yellow, friable membrane and

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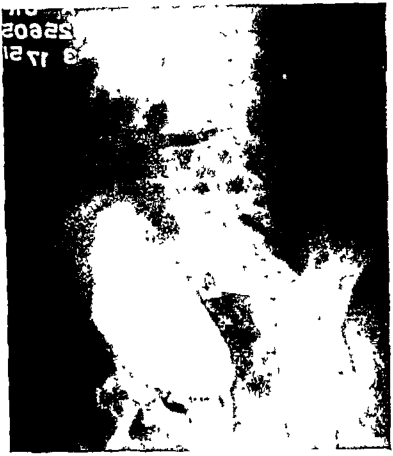

FIG. 2. Cystogram in anteroposterior and oblique views, showing filling defect at vesica apex.

right of the midline of about 6 weeks' duration. About one week previously he noticed painless hematuria; otherwise, there were no urinary symptoms. In 1939 a transurethral prostatic resection for vesical neck contracture had been done with complete and lasting results.

The only abnormal finding on general examination was an area of tenderness and an irregular, rounded mass measuring approximately 7 to 8 cm. in diameter in the lower abdomen just to the right of the midline.

Accessory clinical findings were: hemoglobin, 12.2 gm.; red blood cells 4,010; 000; white blood cells 8,400 with a normal differential. The urinalysis showed cloudy, yellow urine; acid reaction; specific gravity, 1.017; albumin, 1 plus; sugar, negative; and microscopically it was loaded with white blood cells and only 3 to 5 red blood cells. A culture showed no growth of organisms. The nonprotein nitrogen was 37 mg. per cent. The phenolsulfonphthalein showed 60 per cent excretion in 2 hours. The chest film and electrocardiogram were essentially normal. An excretory urogram showed a normal upper urinary tract.

A cystogram showed what appeared to be a rather large diverticulum extending from the dome of the bladder superiorly, and to the left. A large filling defect was noted in the interior of the so-called diverticulum, extending into the dome of the bladder (fig. 2).

On the third hospital day, under spinal anesthesia supplemented with sodium pentothal and curare, a low midline abdominal incision was made, exposing the space of Retzius and the dome of the bladder. The incision was extended superiorly to encircle and include the umbilicus. The tumor mass was conical in shape, somewhat irregular in outline, and hard in consistency. It extended to within 2 to 3 cm. of the umbilicus, and was firmy attached to the transversalis fascia, the peritoneum, and portions of the posterior rectus sheath. The peritoneum superior to the upper extremity of the tumor was opened, and was found to be involved in the process also. The tumor mass was widely excised superiorly, to include a large margin of the peritoneum, transversalis fascia, and rectus sheath. The mass was then dissected inferiorly and freed, and a large cuff of the bladder, approximately 2 cm. in diameter, was removed from the bladder dome at the margin of the tumor. The abdomen was carefully palpated for frank metastases and enlarged intra-abdominal lymph nodes. None was found. The large defect in the peritoneum was then closed with some difficulty.

Except for a wound separation from vomiting on the fifth postoperative day, the convalescence was normal, and the patient was discharged on the seventeenth postoperative day, voiding easily per urethram.

The pathologist's report on the specimen removed at operation was as follows:

"The specimen submitted (fig. 3) consists of a large, somewhat ovoid mass of rubbery, grayish purple tissue which is almost completely enclosed in a smooth, serosal membrane. Beneath the serosal membrane there bulge irregular nodular masses and cystic spaces which appear to contain mucinous material. On viewing the inferior surface of the specimen, one sees that it has been removed from some hollow viscus, and the cut surface encloses a muscular wall upon which is superimposed a velvety mucosa that is raised in irregular, branching folds and is grayish tan in color. There is a small stoma on the mucosal surface, through which project ragged and irregular necrotic strands of tissue and from which oozes a sticky, gelatinous material. Gross sections through the structure reveal the interior to be almost completely occupied by a grayish yellow, necrotic mass of papilliferous tissue which is embedded in a clear, gelatinous material. At several points in the muscular wall of the specimen there are rounded cystic spaces which contain a gelatinous substance. Some of these spaces are seen to be invading the muscularis and to have penetrated beyond it into the superficial adipose tissue.

"Microscopic examinations (fig. 4) show a dense fibromuscular stroma which encloses large and small irregular cystic spaces containing a material that stains

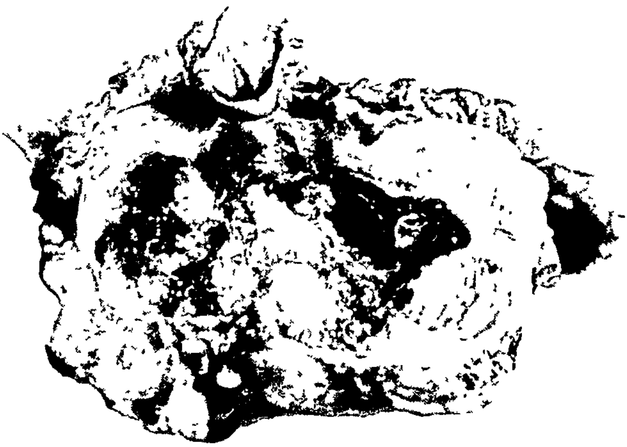

FIG. 3. Specimen removed at operation. Glistening mucin covers cut surface of tumor

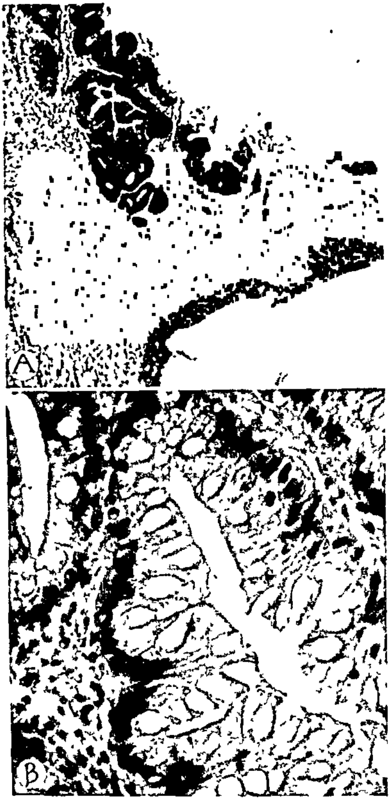

FIG. 4. *A*, low power view of area of transition between normal vesical epithelium and tumor. *B*, oil immersion view of alveolar epithelium. Note mucin-laden goblet cells and nuclear atypism

a pale lavender color. Projecting into these cystic spaces are irregular fronds consisting of a thin, fibrous core upon which are superimposed a tall columnar epithelium, between the cells of which there are interspersed numerous goblet cells. The columnar epithelial cells tend to vary markedly in size, shape and staining reaction, the nuclei of many of them being hyperchromatic. Numerous mitotic figures are seen. In some of the cystic spaces the mucinous content has so distended the interior that the epithelial cells are flattened, many being necrotic and atrophic. Many of these primitive gland-like structures are seen at the periphery of this specimen, having completely penetrated the muscular wall, and are located in the surrounding fibro-adipose tissue. On some of the sections, transitional cell epithelium is seen. This gradually merges into a tall columnar, cylindrical epithelium, which rises in fronds, forming numerous wavy and delicate papillae. Beneath the transitional epithelium there are numerous collections of mononuclear leukocytes. In other areas there is marked edema and desquamation of the transitional epithelium and of the wildly disordered columnar epithelium.

"Final diagnosis (Dr. C. C. Carpenter): Mucinous adenocarcinoma developing in the embryonic remnants of the urachus."

The patient has been followed at regular intervals since discharge, and appears to be doing well. Repeated cystoscopies have shown no evidence of intracystic recurrence. The wound has healed well, and there is no sign of a local recurrence.

SUMMARY

The natural history of mucinous adenocarcinoma of the urachus is reviewed, and the clinical and pathologic findings are discussed.

A case is added to the 49 previously reported cases.

CONCLUSION

It is well nigh certain that the handful of reported cases does not truly reflect the actual incidence of mucinous adenocarcinoma of the urachus. Furthermore, the dearth of clinical information relative to the known cases allows no conclusions as to their relative malignancy, the site of metastases and the rapidity of their occurrence, the radiosensitivity of the tumors, or the prognosis. It cannot be too strongly urged that all cases which are recognized be carefully studied and diligently followed in order that the meager store of knowledge concerning these tumors may be increased.

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URETHRAL STRICTURE FOLLOWING TRANSURETHRAL RESECTION PREVENTED BY INTERNAL URETHROTOMY. PRELIMINARY REPORT OF EXPERIENCE WITH OTIS URETHROTOME*

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Postoperative urethral stricture continues to be troublesome following transurethral resection, although its frequency of occurrence has diminished sharply since the early days of this operation. Most strictures occur in the pendulous or scrotal portions of the urethra and they usually are tough, rubbery, resilient and respond poorly to dilatation. The most common site of stricture is the penoscrotal junction.

The principal cause of postoperative strictures is now generally agreed to be trauma to the urethra from instruments which are of too large caliber to be admitted easily by the urethra. Other possible etiologic factors include irritation from the urethral catheter, postoperative urethritis, trauma to the urethra at the point of junction of its movable and fixed portions (penoscrotal junction) from the up-and-down and side-to side motion of the resectoscope (Stratte and Stratte), excessive heat generated in the sheath of the resectoscope, if the electrourethrotome is used, and a protracted period of operation.

Urethral stricture can be prevented by employing either perineal urethrotomy or a small resectoscope (24F or smaller) if the urethra is too small to accommodate a resectoscope of standard size. Perineal urethrotomy takes advantage of the fact that the bulbous urethra is the portion of the urethra with the greatest caliber. Introduction of the resectoscope through an external urethrotomy boutonniere,† as suggested by Cabot and by Thompson and brought into favor by Nesbit, by-passes the narrower portions of the urethra. Nesbit advised external urethrotomy or use of a small resectoscope in every case in which a 30F caliber steel sound "fails literally to drop into the urethra." In his experience, such a situation is present in approximately 20 per cent of patients who are subjected to transurethral resection.

As mentioned previously, the incidence of stricture following transurethral resection has declined sharply since the early days of the operation. This is the result of such factors as improved surgical technique and instruments, modern chemotherapy and antibiotics and better knowledge of, and respect for, the urethra on the part of the surgeon. Nevertheless, a substantial number of postoperative urethral strictures still is seen. It is reasonably certain, also, that for

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* Abridgment of paper read at the meeting of the American Association of Genito-Urinary Surgeons, Hot Springs, Virginia, May 6 to 8, 1953. The complete paper is printed in the *Transactions of the American Association of Genito Urinary Surgeons.*

† This procedure was also described in 1902 by Wishard.

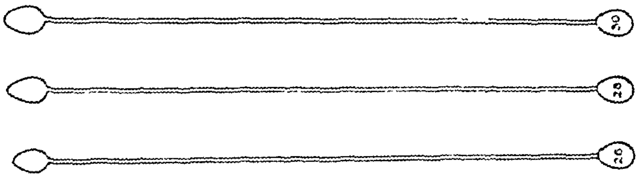

Fig. 1. Otis diagnostic bulbs (bougie à boule)

every patient with such a stricture who presents himself for treatment, there is probably another patient, the caliber of whose stricture is sufficiently large (16 to 18F or larger) so that he voids reasonably well and is satisfied with the result; if such patients should require a further transurethral procedure, however, the stricture would greatly complicate treatment. Causes of most postoperative strictures today, we believe, are two: first, but probably of least importance, is inaccurate preoperative calibration of the urethra; second is the surgeon's hesitation to stop and do external urethrotomy when it is indicated.

Regarding preoperative calibration of the urethra, it is our opinion that minimal urethral narrowing at times may not be appreciated with steel sounds. Too often, in borderline cases, it is difficult to decide whether the sound actually dropped in of its own weight or was helped a little. More accurate calibration of of the urethra is possible with the Otis metal bulbs (bougie à boule; fig. 1). With these bulbs it is possible to detect minimal narrowing from the bulb to the urethral meatus, and in addition, to determine the exact location and length of the narrowed portion; this information is almost impossible to obtain accurately with steel sounds. The slightest "jump" of the bulb, either on introduction or withdrawal, indicates a definite point of narrowing. Such a slight jump when using only the 30F bulb is not infrequently encountered and probably would be unnoticed with a sound. We are convinced that this is the type of case in which so often the resectoscope passes easily, yet becomes snug in the urethra during operation.

The hesitation of the surgeon to employ external urethrotomy when it is indicated stems from the fact that he is anxious to get on with the operation; he dislikes to stop and lose part of the time during which the anesthesia can be expected to last. Ten to twenty minutes, or more, may easily be lost with this procedure, depending on such factors as whether or not the perineum already has been prepared, the availability of the necessary instruments, the training and adeptness of the operating personnel, as well as the familiarity of the surgeon with the procedure. These factors, coupled with the slightly lengthened stay in the hospital and the occasional perineal fistula which may persist for two or three weeks, make the surgeon hesitant to use the procedure, especially in borderline cases.

It would seem, therefore, that if some simpler, safer and less time-consuming procedure could be devised which would overcome this troublesome problem, it would be a boon to both patient and surgeon. We believe that preliminary internal urethrotomy may be the answer to this problem.

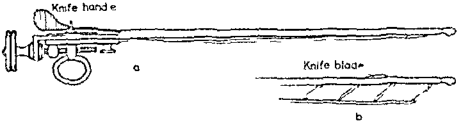

FIG 2 Otis urethrotome, straight model Tip of instrument is equipped with screw threads for attachment to filiform guide if desired In illustration, small metal tip has been screwed on so that instrument can be used without filiform

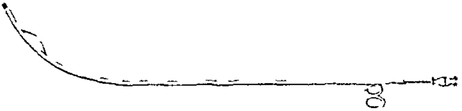

FIG 3 Maisonneuve urethrotome Note screw threads on tip of urethrotome for attachment to filiform guide

INTERNAL URETHROTOMY PRELIMINARY TO TRANSURETHRAL RESECTION

Internal urethrotomy preliminary to transurethral resection was suggested to the senior author (Emmett) by Dr. Harold McDonald of Atlanta, Georgia who has been using this procedure successfully for several years. Also, White and Berry, of Kingston, Ontario, reported use of this procedure in 1946. Our object here is simply to report our experience with the procedure during the past year Sufficient time has not elapsed to enable us to make a final evaluation but we have been pleased with our results.

Choice of treatment —We have employed the Otis urethrotome (straight model; fig. 2) for several reasons It was designed principally for the cutting of strictures of large caliber. In its contracted state it is of 16F caliber and can be expanded (like a Kollmann dilator) so that it can cut as high as 45F. When the straight model is used there is minimal danger of the instrument's entering the membranous urethra, where it could cut the external sphincter. The curved model would tend to engage the membranous urethra, endangering the external sphincter. Inasmuch as practically all narrow portions which require cutting are in the pendulous or scrotal urethra, the instrument is ideal for our purpose Further protection against cutting the external sphincter is provided by the fact that the knife blade does not rise out of its slot until it has been withdrawn about 2 cm from the tip of the instrument Also, the cutting is done "on withdrawal" of the knife rather than when force is exerted in the opposite direction, as with the Maisonneuve instrument (fig. 3) We have been more pleased with the cold cutting blade than with the high-frequency current as, in our experience, often after internal urethrotomy with the Riba electrotome, the urethra immediately contracts or goes into spasm, making introduction of instruments most difficult.

Technique —The technique of the procedure is simple, but it requires accuracy and scrupulous attention to detail As was mentioned, the first step is careful calibration of the urethra with the Otis bulbs (fig 1). The urethra is calibrated up to and including 30F. Any narrowing of the meatus or fossa navicularis is corrected by generous meatotomy, in which the floor of the fossa is cut Following this, calibration is continued. No attempt is made to pass the bulb beyond the bulbous urethra into the membranous urethra. Any evidence of narrowing, including even the slightest jump with the 30F bulb, is regarded as indication for urethrotomy.

The Otis urethrotome is then inserted into the urethra in its closed condition, with the dial and knife slot pointing upward (12 o'clock position of the urethra). The instrument is passed lightly until the tip rests in the bulbous urethra. The object is to make a clean, linear cut in the roof of the urethra to 36F, without avulsing or stretching the urethra. To do this, the instrument is expanded slowly and carefully until it is just comfortably snug, following which the knife is withdrawn through the length of the urethra with a brisk, determined motion, so that it will cut cleanly. Explanation of why too much cutting does not result will be made a few lines farther on. If this cut was of less than 36F, the blades are closed, the knife is returned to the "home" position and the procedure is repeated until the final cut has been made with the urethrotome blades expanded to 36F, as shown on the calibrated dial. In most cases, this is accomplished in one to three maneuvers. All cuts should be made with the knife at the 12 o'clock position, in the hope that the cut may be in the septum and that the paired bodies of erectile tissue of the corpora cavernosa penis may be avoided. Care must be taken not to overstretch the urethra by expanding the blades of the urethrotome; otherwise the same trauma would occur as that which occurs with the forcing of too large instruments through the urethra. Following the urethrotomy a 30F sound is passed into the bladder to evaluate the membranous and prostatic urethra. The resectoscope is then passed.

After the resection has been completed, we leave a 26F two-way irrigating Foley bag catheter indwelling for 48 to 72 hours. This is to allow the incision in the urethra to seal over and partially heal, before the patient voids through it. This procedure, plus administration of antibiotics (penicillin and streptomycin) 24 to 48 hours before, and for 4 to 6 days after operation, we believe has, been important in prevention of febrile reactions. We have been most pleased with the ease of movement of the resectoscope in the urethra throughout the operation following urethrotomy. As every transurethral surgeon well knows, there is nothing that so contributes to the ease of resection as an adequate urethra and a freely moving resectoscope.

Regarding healing of the urethrotomy incision, we agree with the opinion of White and Berry that, in the absence of postoperative sounding, the incision probably heals in such a manner that the original caliber of the urethra is restored. Prolonged periods of use of large, indwelling catheters, or postoperative periodic use of large sounds, may result in a urethra of larger caliber.

EXPERIENCE WITH INTERNAL URETHROTOMY

In the past year (since May 1, 1952) internal urethrotomy with the Otis urethrotome has been done by the senior author (Emmett) in 59 cases. In 50 of these the procedure was done preliminary to transurethral prostatic resection, which represents an incidence of approximately 20 per cent of the transurethral resections performed by the author during the period designated In 3 cases it was done preliminary to transurethral removal of a vesical tumor In the remaining 6 cases* the urethrotomy was performed as treatment of bona fide urethral stricture

FIFTY-THREE CASES IN WHICH INTERNAL URETHROTOMY WAS DONE PRELIMINARY TO A TRANSURETHRAL SURGICAL PROCEDURE

As has been mentioned in this paper, there is no agreement as to the distinction between a bona fide stricture and a small normal urethra For clarity we have made the following arbitrary definitions If the caliber of the urethra is 26F or larger, and if there is no history of previous disease or trauma which might have caused stricture, we have classified the urethra as a small normal one On the other hand, if the caliber of the urethra is 24F or smaller, or if there is a definite history of previous urethritis or trauma which could have caused stricture, either or both, we have classified the urethra as one in which there is a stricture On the above basis, of the 53 urethras, 37 were classified as small normal and 16 were said to be strictured

Four of the 53 cases require some individual explanation In 2 cases, a 30F bulb seemed to pass freely, yet the resectoscope became a little snug after the resection had progressed for a few minutes, therefore, the resectoscope was withdrawn and urethrotomy was done, cutting to 36F In 1 of the 2 cases, the resectoscope moved freely during the remainder of the operation In the other, it again became slightly snug near the end of the operation We feel that probably we were a little inaccurate in calibration in these cases The other 2 cases of the 4 which require explanation were as follows In 1, the urethra was cut before operation (at the penoscrotal junction) from 26 to 35F, following which a 30F bulb passed easily and the resectoscope passed easily In spite of this, the resectoscope became a little snug toward the end of the operation but not enough to require further urethrotomy In the other case, the urethra was cut from 24 to 34F, in spite of which the resectoscope became so snug in the course of the operation that it was removed and the urethra was cut to 36F Following this, the resectoscope moved freely throughout the entire operation (We now cut the urethra in all cases to at least 36F)

We have encountered no troublesome bleeding from urethrotomy During resection the pressure from the sheath of the resectoscope apparently has been sufficient to control bleeding, as has the presence of the 26F indwelling bag catheter, postoperatively In only 1 case did we find it necessary to put a compression bandage on the penis to make pressure against the catheter and in this case the bleeding was not excessive We have not observed pain or discomfort as a result of the procedure

We have noted no increase in the incidence or severity of postoperative febrile reactions This no doubt is partially attributable to our routine use of antibiotics, which was previously described Another factor may be the two way irrigating

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* The 6 cases in which urethrotomy was done for stricture will not be discussed here, but they will be represented in the complete article published in the *Transactions of the American Association of Genito Urinary Surgeons*, 1953

Foley bag indwelling catheter, our use of which also has been described; it may minimize the possibility of absorption into the general circulation during voiding.

Patients usually are allowed to leave Rochester on the twelfth to fourteenth postoperative day. In each case, 2 days before their departure, we have passed a 26 or 28F sound and, in every case, the sound has passed easily and freely. A 30F sound has not been used, to avoid unnecessary discomfort to the patient.

Late results and complications.—Inasmuch as all of the patients concerned in this report have been operated on in the course of the past year (since May 1, 1952), long-term follow-up has not been possible. In our experience, however, most postoperative strictures become apparent within six months; hence, this preliminary report may have more significance than would appear from a cursory survey. Patients who live near Rochester have been asked to return periodically for urethral calibration. Letters have been written to the remaining patients and their physicians, requesting that calibration be carried out at home. We soon learned that patients who are having no trouble voiding are not anxious to submit to the discomfort, even if only minimal, of having a sound passed through the urethra. For this reason our follow-up response has not been as prompt as we would like it to be. In spite of this, we have been able to secure results of follow-up study on 24 of the 53 patients; 10 returned to the clinic, while 14 were examined by their home physicians. Of these 24 cases, 11 represent a follow-up period of six to ten months; 7 represent a follow-up period of three to six months; 3 represent a follow-up period of two to three months, while in 3, the follow-up period was less than two months.

Before we give the results of this study, however, we wish to report that none of the 53 patients has written complaining of any difficulty with the urinary stream. Metal Van Buren sounds, caliber 26 or 28F, have been passed through the urethras of all 24 who have been followed and in only 1 was any evidence of urethral narrowing found. Larger sounds were not passed because of discomfort to unanesthetized patients. We have employed sounds rather than diagnostic bulbs in order that the prostatic urethra and vesical neck could be calibrated at the same procedure. In the cases in which we ourselves have been able to make the re-examination, we have been impressed with the adequacy of the urethra.

We have been especially interested to know whether any late manifestations of fever or sepsis are likely to occur as a result of this procedure. As far as we can determine, only 1 patient has had a delayed febrile reaction. This was a man who had an extensive infiltrating carcinoma of the bladder for which, on many occasions, he had received transurethral fulguration and radon seeds had been implanted. As a result of this instrumentation, a dense stricture of approximately caliber 16F had developed at the penoscrotal junction. For the purpose of inserting an instrument for fulguration of a recurrent tumor, internal urethrotomy was done. The catheter, however, was left in place for only 2 days. This probably was not sufficiently long because after he had returned home he was ill in a hospital for two to three weeks with recurring fever. There were no localizing signs, however, and the fever gradually subsided. We now would treat such a patient in our routine manner, using antibiotics and an indwelling catheter. These measures, we believe, would have prevented the complication.

Although we have had no serious complications in our past year's experience with internal urethrotomy, we feel certain that sooner or later we will encounter some troublesome complications such as bleeding, infection, or even sepsis. Nevertheless, we also are of the opinion that, with careful technique and attention to details, complications should be minimal and should not seriously detract from the great advantages of the procedure.

PAST HISTORY OF INTERNAL URETHROTOMY

The past history of internal urethrotomy (done chiefly for urethral stricture) is most interesting in the evaluation of its modern revival. A summary of this is included in the unabridged article.*

SUMMARY AND COMMENT

There are two important indications for internal urethrotomy: 1) the presence of resilient strictures, especially those of the pendulous and scrotal urethra, which will not permit adequate dilatation,† and 2) the need to enlarge the pendulous and scrotal urethra (either a small "normal" urethra or definite stricture) to permit the passage of large operating instruments, such as the resectoscope and the lithotrite, without the production of subsequent postoperative stricture. We believe it possible that internal urethrotomy may gradually replace perineal urethrotomy when transurethral resection must be performed through a urethra of small caliber. Whether or not this prediction is sustained will depend largely on care and scrupulous adherence to details by the surgeon, to prevent untoward complications. It must be remembered that, by internal urethrotomy, an opening may be made into large venous channels such as those of erectile tissue, permitting even more ready access of foreign material and infection into the general circulation than does the prostatic capsule during transurethral resection. Because of this, the same precautions shown to be effective in transurethral resection should be adhered to, namely administration of antibiotics 24 to 48 hours before, and for several days after, operation as well as adequate care devoted to drainage by indwelling urethral catheter for at least four days. Such drainage permits the urethral incision to seal over, and prevents the patient's voiding into the general circulation via the cavernous tissue or an unhealed urethra. If such precautions are scrupulously observed, it is our opinion that the procedure will prove to be of such minimal risk that it may be employed before transurethral resection whenever desirable. Whether or not further experience, with benefit of modern technique and suitable precautions, will enlarge the indications for the procedure in the presence of urethral stricture remains to be seen.

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[*] Published in the *Transactions of the American Association of Genito Urinary Surgeons* 1953.

[†] Full discussion of this will appear in the unabridged paper in the *Transactions of the American Association of Genito Urinary Surgeons* 1953.

increased in size. Later, one of them underwent suppuration, ruptured spontaneously, with the subsequent development of a urinary fistula on the ventral aspect of the penis. Following this, there had gradually developed through the urinary fistula a cauliflower-like ulcerative and proliferative lesion. A short time prior to admission he received 24 capsules of aureomycin. He noticed little or no improvement from this therapy. At the time of admission he also complained of difficulty and discomfort on urination. He stated that most of the urine was passed through the urinary fistula. He had some fever during the present illness, but had no weight loss. At times there had been some bleeding from the lesion.

Physical examination was essentially negative except for the following findings: On examination of the genitalia there was a cauliflower-like lesion on the ventral aspect of the penis, measuring about 4 or 5 cm. in diameter. There was considerable swelling of the entire penis in the neighborhood of this lesion, with numerous associated sinus tracts, all draining a thick, purulent exudate (fig. 1, *A*). The foreskin was not retractable; however, thick pus exuded from beneath the fore-

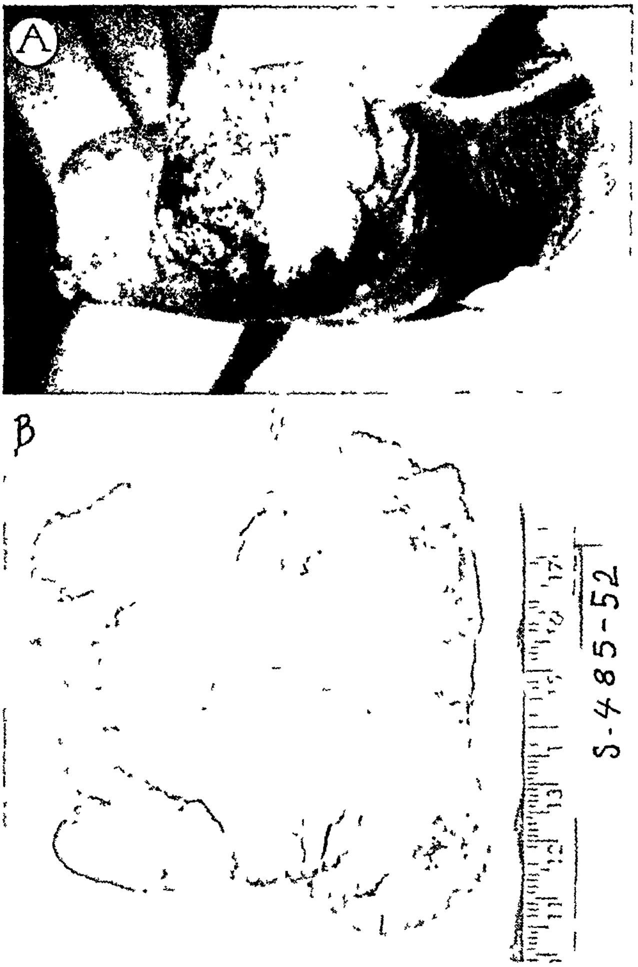

FIG. 1. *A*, penile lesion showing large verrucous growth with numerous associated sinus tracts *B*, penile lesion showing extension and penetration into corpus spongiosum and cavernosum urethrae

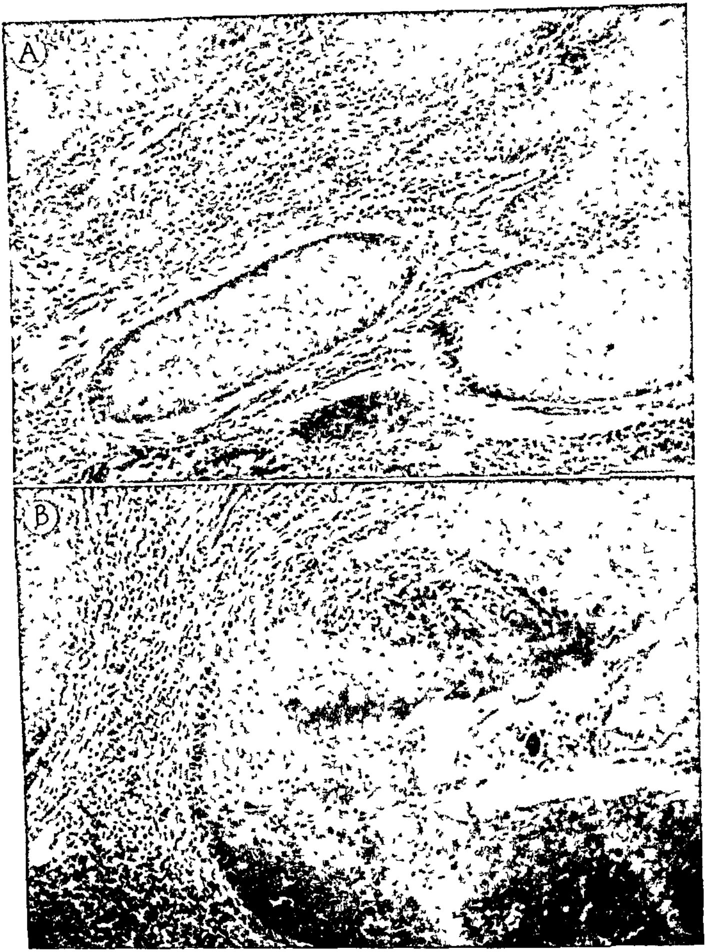

FIG 2 *A*, section of lesion showing thickened keratotic stratified squamous epithelium with downgrowth and occasional atypical anaplastic cells *B*, section of lesion showing thickened keratotic stratified squamous epithelium overlying chronic suppurative inflammation

skin and from the external urinary meatus The inguinal glands were barely palpable The blood count showed 4 20 red cells, 13,000 white cells, with a normal differential Urinalysis showed 1 plus albumin, 10–15 red cells per high power field, 70 to 80 white cells per high power field Serology was negative X-ray of the chest showed no abnormality

On admission to the urological section, a tentative diagnosis of carcinoma of the urethra and penis was made. On May 7, 1952, a suprapubic cystostomy was done, and a biopsy of the penile lesion was taken. Also at the time of cystostomy a small cauliflower-like lesion was removed from the vesical neck for biopsy. Postoperative course following cystostomy was uneventful. The biopsy report showed no evidence of carcinoma. All specimens showed condyloma. On June 3, 1952, circumcision was performed with the electric cautery and all of the proliferating tissue was excised from the penis with the electrosurgical unit. At the time of this procedure it was evident that the condylomatous lesion had invaded the corpora cavernosa. At the time of this operation an inguinal lymph node was also removed for biopsy. Biopsy report showed typical condylomatous changes in the tissue removed from the penis. There was no evidence of malignancy in the biopsy report of the lymph node. These sections were reviewed by the Armed Forces Institute of Pathology, and the report returned stated that the sections were typical condylomata and showed no evidence of malignancy. Sulfonamides and terramycin were given but apparently had no effect on the condylomatous lesions. A course of fuadin was given, and this, likewise, produced no appreciable improvement. Podophyllin ointment was applied locally and seemed to have little or no effect.

Finally, after all of these conservative measures had been of no help, it was decided that the only course left that might cure this condition would be a subtotal amputation of the penis. This was done on September 24, 1952. At the time of amputation several small condylomata presented in the stump of the urethra. These were electrocoagulated. The postoperative course was uneventful. On October 9, 1952, 18 through 24F sounds were passed easily through the urethral stump. A No. 18 Foley catheter was passed through the urethra into bladder and left indwelling. The suprapubic catheter was removed. The suprapubic sinus healed promptly. The urethral catheter was then removed. The patient was able to void satisfactorily with perfect control. The penile stump was well healed and clean. He was discharged October 15, 1952.

He was seen subsequently on several occasions to dilate the urethral orifice. Approximately 3 months following discharge from the hospital it was noted that there was a recurrence of condyloma surrounding the urethral opening on the amputation stump. He was re-admitted to the hospital on January 7, 1953; a spinal anesthetic was given, and the urethra inspected with a panendoscope. The urethra was filled completely with condylomata from the bladder neck to the external opening on the penile stump. The resectoscope was introduced and the condylomata were fulgurated completely. An indwelling urethral catheter was inserted and allowed to remain in place for several days. Upon removal of the catheter the patient was able to void well and had normal sphincter control. This time, following discharge from the hospital, there was considerably more difficulty dilating the external meatus. Within 3 months another recurrence of condyloma developed in the vicinity of the urethral orifice. On April 15, 1953, the patient was given pentothal for anesthesia and the urethra was again inspected with the panendoscope. The urethra was clean except for a few condylomata within the distal 1–2 cm of the urethra These were fulgurated as before An indwelling urethral catheter remained in place for several days and was then removed Upon removal of the catheter he voided well with normal control He was discharged from the hospital April 22, 1953 Subsequently there was marked contracture of scar tissue surrounding the urethral orifice, producing a filiform stricture at this point He was re-admitted to the hospital, and on May 22, 1953, under pentothal anesthesia, the scar tissue was excised from the region of the urethral orifice and the urethral stump was freshened by excising a few millimeters from its margins The freshened urethral mucosa was then sutured to freshened skin edges of the penile stump A 24F indwelling urethral catheter was inserted and remained in place for one week before removal One week following removal of the catheter a 28F sound could be inserted easily He was discharged on June 11, 1953 He had been seen on several occasions since that time A 28F sound can be introduced into the urethra with ease, and there has been no evidence of recurrence of condylomata

SUMMARY

A case of extensive condyloma of the urethra is presented The entire urethra, from the bladder neck to the external urinary meatus, was involved Grossly, the lesion demonstrated marked invasive characteristics, involving and destroying considerable portions of the corpora cavernosa and corpus spongiosum Microscopically, however, there was no evidence of malignancy, several adequate biopsies showed a picture typical of condyloma accuminatum This lesion was controlled only after subtotal amputation of the penis and transurethral fulguration of condylomata in the remaining portion of the urethra

There is a paucity of reports of similar cases in the literature However, urethral condylomata are probably more common than these reports would indicate This lesion should probably always be considered when one encounters recurrent condylomata in the vicinity of the external urinary meatus and in cases of resistant so called nonspecific urethritis with persistent, purulent urethral discharge Earlier recognition and adequate treatment might prevent progression to the point observed in the case herein described

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SURGICAL TREATMENT OF SEVERE LYMPHEDEMA OF PENIS

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Lymphedema of the penis may develop as the result of chronic regional lymphatic obstruction following 1) granulomas such as chancroid, tuberculosis, syphilis, lymphopathia venereum or granuloma inguinale, 2) removal of inguinal lymphatic glands or mutilating operations such as is required for peri-urethral phlegmon, or 3) inflammation of the lymphatics.[1, 2] Likewise, lymph stasis resulting from filarial infestation may cause brawny edema of the penis of extensive proportions.

Penile lymphedema is usually seen in conjunction with a like process in the scrotum, but may however occur without involvement of the latter. Severe lymphedema (elephantiasis) produces not only a very unsightly deformity but may also become a source of extreme mental anguish when the afflicted person finds himself deprived of a normal sex life.

The purpose of this paper is to report on an operative technique to correct the deformity in penile elephantiasis. We have performed the operation on 4 patients with gratifying results.

With the patient under spinal anesthesia, the penis, scrotum, perineum, groins, lower quadrants of the abdomen and thighs are prepared surgically. A circular incision is made at the base of the penis and deepened down to Buck's fascia (fig. 1, *A*). A longitudinal incision is then made along the dorsum of the penile shaft, extending from the circular incision to the tip of the prepuce. This is deepened through the hypertrophied skin and edematous subcutaneous tissue to Buck's fascia (fig. 1, *B*). The glans, which is usually embedded in the edematous mass, is exposed by a dorsal slit. Another circular incision is now made at the coronary sulcus 2 mm. proximal to the glans, leaving a cuff of coronal mucosa just wide enough to permit suturing of the graft (fig. 1, *C*). A wider cuff is avoided for this may later develop into an edematous ring and cause difficulty during coitus. The diseased skin and subcutaneous tissue between the two circular incisions are then peeled from the underlying fascia, thus denuding the penis. Meticulous hemostasis is observed at this stage.

A split-thickness graft (0.015-0.017 inches) is taken with the aid of a Padgett-Hood dermatome from one of the prepared thighs. This is wrapped snugly around the stripped penis and the excess portions trimmed. At each end, the graft is sutured to the adjacent skin and mucous membrane by mattress sutures using No. 00000 silk material, leaving the loose ends free (fig. 1, *D*, *E*). The graft is so placed that the opposite margins meet on the ventral surface where they

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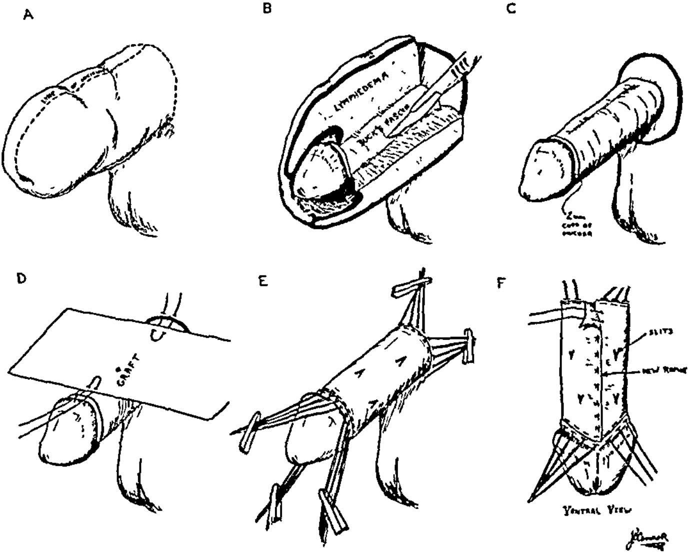

FIG. 1. Operative technique for correction of severe penile lymphedema

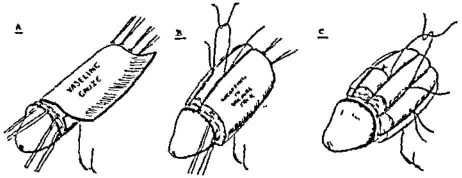

FIG. 2. Application of stent pressure dressing

are approximated by silk mattress sutures (fig. 1, *F*). Several stab openings are made in the graft to ensure drainage.

A layer of vaseline gauze is applied to the grafted area, and a one inch vaginal pack is then wrapped over this dressing. The loose ends of the sutures at each end of the graft are then tied together (fig. 2), thus providing a stent pressure dressing.

If the scrotum is also involved in the elephantoid process, a plastic resection of the excess skin and subcutaneous tissue is made prior to the procedure on the penis.

A 18F Foley catheter is placed in the urethra for the first 10 days. Administration of antibiotics is advisable. Ten milligrams of stilbestrol every 6 hours should be given during the first week in an attempt to prevent erections. Two

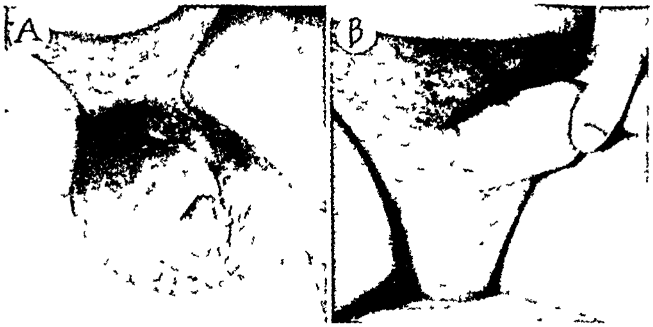

FIG. 3. Case 1. Severe lymphedema of penis and scrotum. *A*, before operation. *B*, 9 months after operation.

per cent neomycin solution is applied to the dressing at intervals to minimize infection.

The stent and dressings are removed in 10 days and if the wound is dry and healed, the sutures are removed.

CASE REPORTS

Case 1. P. A., a 47 year old Puerto Rican, admitted to the Fourth Division Urology Service, Bellevue Hospital, was first seen February 20, 1953, complaining of swelling of the penis and scrotum for 2 years. During the past 10 years, he had also noted marked enlargement of his right lower extremity.

The scrotum was enlarged to about the size of a grape fruit. The skin was thick and coarse, with a wart-like surface. The penis was similarly involved and measured 15 cm. in circumference (fig. 3, *A*). The glans was not visible but could be felt buried within the edematous mass. Several nocturnal searches for filarial parasites in the blood were negative.

On March 4, 1953, the greater part of the scrotal sac was extirpated, preserving the unaffected testicles, and leaving sufficient skin for a new scrotum. The diseased skin and subcutaneous tissue covering the penis were excised down to Buck's fascia. The penile contents within the fascia were normal in appearance. A split-thickness graft from the thigh was then applied to the denuded area.

The dressings were soaked with 2 per cent neomycin solution daily. On the tenth postoperative day, the dressings were removed and a 90 per cent take was observed. Both the penis and scrotum were restored to normal size.

Microscopic sections of the removed specimen revealed focal chronic inflammatory reaction, edema and fibrous thickening of the dermis and subcutaneous tissue. Several foci of foreign body giant cell reaction were present.

The last follow-up examination of this patient was 9 months after operation. His genitalia were of normal size (fig. 3, *B*). The penile skin was soft and easily stretched during erections. Sexual relations were completely satisfactory.

Case 2. L. D., a 23 year old man, was admitted to the Fourth Division Urology Service, Bellevue Hospital on May 12, 1953. He gave a history of intractable pruritus of the scrotum which had persisted for 5 years despite various dermatologic treatments. For the past 2 years, the penis had been progressively increasing in size so that intromission was no longer possible.

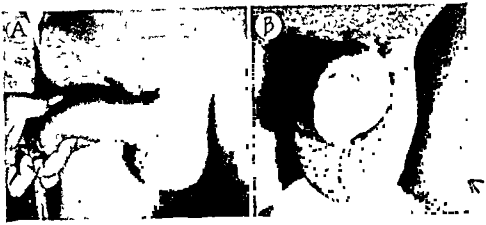

FIG. 4. Case 2 Penile elephantiasis. *A*, before operation. *B*, 6 months after operation. Note development of cuff of edematous tissue at corona. This is prevented by excising as much of coronal mucosa as possible.

Examination disclosed a penis shaped like a bowling pin. The distal four-fifths exhibited a fusiform swelling while the base retained its normal proportions (fig. 4, *A*). The penis measured 17 cm. in circumference at its largest portion. The skin was thick and edematous, although fairly smooth on the surface. The scrotum was slightly enlarged and was covered by a chronic lichenified eczema.

On May, 15, 1953, the lymphedematous penile skin and subcutaneous tissue were removed down to the fascial plane and a split-thickness graft from the thigh applied to the raw area. The patient experienced episodes of painful priapism following operation despite 10 mg. stilbestrol every 6 hours. Daily soaks with neomycin solution were instituted. Upon removal of the dressings on the tenth day, the graft take was over 90 per cent.

The removed specimen was 3.5 cm. thick at its widest point. Microscopic sections of the skin and subcutaneous tissue revealed a great proliferation of collagenic type connective tissue. There were focal collections of lymphocytes in the dermis. The pathological diagnosis was chronic inflammatory reaction with fibrosis.

The patient was last seen 6 months after operation. The penile shaft, except for a cuff of edematous tissue at the corona, was of normal size (fig. 4, *B*). The patient was completely satisfied with the results of the operation and reported he had been able to resume coitus.

Case 3. J. M., a 71 year old man, admitted to the Fourth Division Urology Service, Bellevue Hospital, complained of marked swelling of the penis and scrotum of ten years duration. The patient had never been out of the United States, and the enlargement of his genitalia was not accompanied by any known lymphangitis. In 1943, he was admitted to Johns Hopkins Hospital in Baltimore, where a left hydrocele was found associated with the edema of the penis and scrotum. The hydrocele was repaired, but no improvement in the lymphedema was observed.

The penis and scrotum were greatly enlarged and covered with a thickened indurated brawny skin. A plastic resection of the scrotum was done and the penis stripped of its covering in the manner described. The graft that was subsequently applied had an almost 100 per cent take and the cosmetic appearance of the penis at the time of hospital discharge was excellent.

Case 4. L. Z., a 79 year old man, was admitted to the Fourth Division Urology Service, Bellevue Hospital on May 24, 1953 with an extensive phlegmon involving the perineum, scrotum and penis of three days duration. A perineal urethrostomy and multiple incisions and drainage were done soon after admission. Postoperatively, he had a septic course and marked local infection, which were gradually brought under control by intensive antibiotic therapy. After 2 weeks, the perineal catheter was replaced with a urethral catheter.

Two months after the first operation, there was still a wide granulating area in the scrotum which was epithelizing very slowly. The penis was enlarged to about three times its normal size. It was apparent that the lymphatic drainage of the penis was impaired by cicatricial contraction at the site of the multiple incisions at the base of the penis.

On July 9, 1953, all the hypertrophied tissue in the phallus superficial to Buck's fascia was removed and replaced with a split-thickness graft. Upon removal of the dressings 10 days later, some sloughing was observed at the ventral surface. Epithelization over this defective area however occurred. After removal of the indwelling catheter, the patient voided well. The patient has been seen in our out-patient clinic several times and has not shown any evidence of recurrence in the penile enlargement.

DISCUSSION

The literature on surgical correction of severe lymphedema of the penis is scarce. DeSavitsch described procedures employed on natives of Belgian Congo in which the skin of the penis was removed in the same manner as we had described,[3] but he did not employ skin grafts. Within a comparatively short time, granulation tissue covered the area and proliferation of epithelium from the border of healthy skin occurred, eventually giving the patient a satisfactory functional penis. Ross similarly suggested removal of the involved skin and covering the denuded area with scrotal or thigh flaps. McDonald and Huggins advocated bilateral scrotum-to-thigh anastomoses in an effort to create new lymphatic pathways for drainage of scrotal lymph via the uninvolved thighs.[4] The operation was observed to have helped the scrotal edema but slight penile swelling persisted.

Complete excision of the involved skin and subcutaneous tissue *en masse* down to the underlying muscles and coverage with split-thickness dermatome grafts have been described by various authors for the surgical correction of elephantiasis of the extremities.[5-8] Pratt reported no recurrence of lymphedema of the extremities in 25 patients following this procedure.[9] Inasmuch as elephantiasis of the penis has a similar pathogenesis, an application of this technique to correct the penile deformity seems warranted. Our series, although small, furnished such encouraging results that this procedure offers great promise for a satisfactory solution to severe lymphedema of the penis

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SUMMARY

A surgical method to correct the deformity of severe lymphedema (elephantiasis) of the penis is described It consists of complete excision of the diseased skin and subcutaneous tissue and application of a dermatome split-thickness graft over the denuded area

The technique was utilized in 4 cases with gratifying results There has been no recurrence in lymphedema

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KAPOSI'S SARCOMA OF THE PENIS

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Kaposi's sarcoma of the penis is a rare condition. According to Herbut[1] only 2 cases have been reported so far; both by Barringer and Dean[2] in 1935. Herbut goes on to say that Kaposi's sarcoma was originally described as multiple idiopathic hemorrhagic sarcoma. It is a slowly but chronically progressive cutaneous lesion that usually starts in one lower extremity, but some time during its course becomes bilateral and symmetrical. While there is some difference of opinion regarding the nature of the disease, it is now generally considered to be an angiosarcoma.

The microscopic appearance of Kaposi's sarcoma varies from patient to patient and may resemble a hemangioma, a fibrosarcoma, or a granuloma depending upon whether vascular tissue, fibrous tissue, or inflammatory tissue predominates.

CASE REPORT

J. P., a white man, aged 20, was first seen on March 6, 1953. His chief complaint was swelling and pain in the penis. He stated that on January 24, 1953, while at work he fell astride a bolt protruding from a plank. The next day he felt pain and swelling in the right side of the penis. Examination revealed an area 2 by 3 cm. purple-red in color at the base of the penis on the right side. The entire right corpora cavernosa was indurated and thickened causing a partial erection and bending of the penis to the left. A preliminary diagnosis of thrombosis of the right corpora cavernosa due to his injury was made and arrangements for hospitalization and more complete study were agreed to by the patient. However, he failed to enter the hospital and was not seen again until May 20, 1953. At this time he was brought to the hospital on a stretcher.

Examination at this time revealed that the patient had lost considerable weight. It was evident that he was extremely anemic, and in considerable pain. On examination of the penis the swelling and induration had increased materially causing an increase in the semi-priapism. There was no difficulty in voiding and no residual urine. An area, 6 by 4 inches, on the anterior surface of the left thigh was doughy, reddened, and edematous on the surface but fibrotic underneath. A similar area over the biceps of the left arm about 2 by 2 inches in diameter, another similar condition over the biceps of the right arm, and an area 4 by 5 inches over the right inguinal area and upper right thigh were found. The general physical examination was negative except for changes already described. The family history was irrelevant. It was now apparent that the original diagnosis was in error. Tissue from each area was secured by biopsy and the following report

Accepted for publication November 3, 1953.

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[1] Herbut, Peter A.: Urological Pathology. Philadelphia: Lea & Febiger, 1952, vol. 2. p. 866.

[2] Barringer, B. S. and Dean, A. L.: Kaposi's disease of the penis. Trans. Am. Assoc. Genito-Urin. Surg., **28:** 409, 1935.

was received from Dr A J Miller, pathologist at Corwin Hospital, Pueblo, Colorado

"The biopsy from the base of the penis consisted of two firm, somewhat friable yellow-red mottled fragments of tissue, each measuring 1 by 0 7 by 0 5 cm The mass from the left arm is a lobulated firm mass measuring 5 by 3 5 by 1 7 cm It is covered by thin adhesions torn with difficulty and has a mottled pink grey to dark purple grey color On section some hemorrhage is present, and the tissue is not friable The mass in the right groin measures 3 by 2 5 by 2 5 cm and resembles the mass taken from the left arm The biopsy from the left leg consists of four small to large fragments of light red-grey tissue measuring from 0 5 cm in greatest diameter to 2 2 by 2 2 by 1 cm

"Microscopic The biopsy from the base of the penis consists of dense fibrous tissue replaced by hyaline-like necrotic tissue infiltrated by a small amount of granulation tissue Some acute inflammatory infiltration is present, as well as some hemosiderin filled macrophages In this connective tissue is found a number of closely adjacent tiny capillary spaces lined by neoplastic cells with large nuclei, most of which have enlarged nucleoli A few distinctly atypical mitoses are present among these neoplastic endothelial cells Some skeletal muscle is present The other biopsies show large areas of necrotic tissue mingled with cellular connective tissue Also noted is an infiltrating vascular type of infiltrating neoplasm composed of many capillary channels lined by neoplastic endothelium identical to that seen in the biopsy from the penis The neoplastic endothelial cells are quite large, having large nuclei varying markedly in size, shape and staining quality and containing definitely enlarged nucleoli Distinct atypical mitoses are present Extensive hemorrhage is found in the necrotic areas where the neoplastic tissue is invading and there is no definite encapsulation In other areas invasion by this neoplastic lesion into skeletal muscle is seen The histologic features in all these biopsies are those of an angiosarcoma being accompanied by extensive hemorrhage and necrosis Angiosarcoma in biopsies from base of penis (fig 1, *A*), left arm (fig 1, *B*) right groin, and left leg "

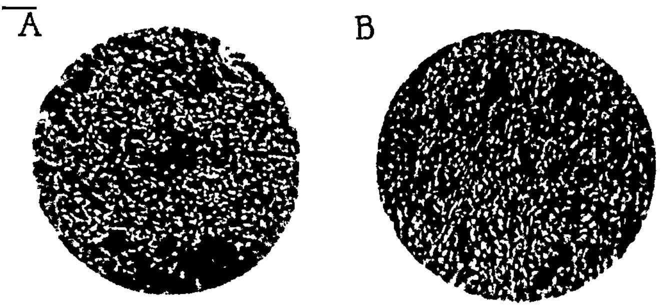

FIG 1 *A*, angiosarcoma section taken from biopsy of penis showing vascular pattern of primary lesion *B*, section from metastatic lesion of left arm showing infiltration into skeletal muscle

Blood count on admission showed 2,370,000 red blood cells, 12,300 white blood cells, hemoglobin 8.5 gm. (basophile 1, eosinophile 10, segmenters 64, lymphocytes 14, monocytes 11). Up to May 20 the patient received five blood transfusions with only temporary relief. Surgery was out of the the question and being of connective tissue origin deep x-ray was not advised. He deteriorated rapidly and died August 19, 1953. Autopsy was denied by his family.

This young man came under State Compensation insurance. The Commission was very reluctant to accept responsibility after receiving the diagnosis of angiosarcoma until the following opinion was submitted. This quotation is from a Symposium on Medicolegal Problems presented under the co-sponsorship of the Institute of Medicine of Chicago and the Chicago Bar Assocation.

"Whatever view we take of the medical opinions, they are frankly, and at best, but theories, but taking them as they are, in connection with the facts heretofore narrated, and taking a common sense, practical view, as courts and commissions must take of the ordinary happening of life, boiled down to its last analysis the medical theory is that there is a relationship between the receipt of injury and origin of sarcoma, and that the degree of injury plays no important part. With this in mind we find a perfectly healthy, strong man who has never lost any time from work, or complained of any illness, suffers an injury and from that time on is incapacitated, grows worse and worse, sarcoma develops at the point of injury from which he dies. The lay mind, under such circumstances, can reach no other conclusion than that reached by the Commission, viz: that the sarcoma was either caused by the injury or was aggravated by it."

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HYALURONIDASE TREATMENT OF SCROTAL HEMATOMA

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Injury or operation on the scrotum frequently gives rise to painful complications scrotal hematoma and hematocele, due to rupture of blood vessels in the area, with extravasation of blood into scrotal tissue, or the cavity of the tunica vaginalis testis, or around it The looseness of the structures and the dependent position of the part predispose to the accumulation of blood, which clots readily to form a tumor like swelling Since the clot is resorbed very slowly, over a period of many weeks, the hematoma causes the patient discomfort and may easily become infected or have other serious consequences [1, 2]

After operation a tight scrotal suspensory, applied immediately, may prevent excessive swelling and relieve some of the pain, but after injury formation of a hematocele or hematoma may be so rapid that such measures are inadequate Removal of the thickly clotted blood by aspiration is almost always difficult and in many cases impossible

The success reported[3-10] with use of hyaluronidase, the "spreading factor," in the dispersion of hematoma and edematous swellings about the face, neck and other parts from injury, operative trauma and disease, suggested the possible usefulness of this enzyme to lessen the viscosity of the extravasated blood and promote diffusion and more rapid resorption of hematocele through the hydrolyzing action of the hyaluronidase on the intercellular cement substance

The present small number of cases includes 4 cases of scrotal injury by external violence, 2 cases of postoperative hematocele (one following hydrocelectomy and the other after vasectomy), and 1 case of spontaneous scrotal hematoma for which no cause could be found Results of treatment were so dramatic as to merit report

In all cases treatment was started within seventy-two hours after onset of the swelling

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[2] Cowdery J S et al Massive hematocele threatening life by exsanguination J Urol, **64** 524–28 1950

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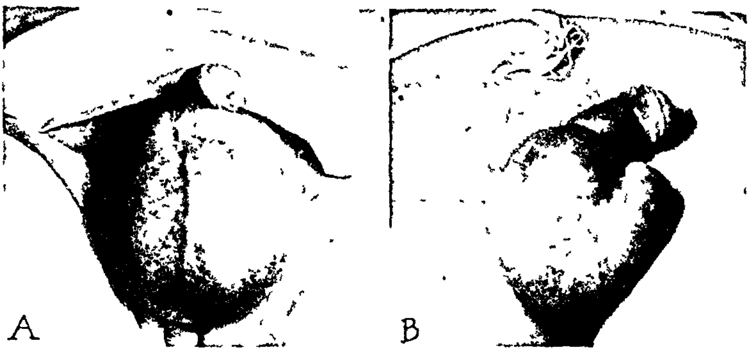

FIG. 1. *A*, traumatic hematoma and swelling of scrotum, of 72 hours' duration. *B*, traumatic hematoma and swelling of scrotum, 24 hours after injection of hyaluronidase. Decided reduction of swelling with definite symptomatic relief.

METHOD

The scrotum, suprapubic region and the inner aspects of the thighs were shaved. The skin of the scrotum over the swelling was cleansed with aqueous solution of zephiran chloride. A wheal was raised in the skin with 1 per cent procaine, and a 15 gauge needle was introduced into the hematoma to aspirate as much as possible of the contents.

The treatment solution was prepared by combining 300 TR (turbidity-reducing) units of hyaluronidase,* 300,000 units of aqueous crystalline penicillin and 5 cc of 1 per cent procaine in normal saline for a total of 30 to 50 cc of solution. The amount depended on the size of the swelling to be reduced. This solution was injected into the hematoma and a tight adhesive suspensory was applied.

In 3 patients the spermatic cord was infiltrated with 5 to 10 cc of 1 per cent procaine prior to strapping.

The suspensory was left in place for twelve to twenty-four hours, after which a lighter suspensory was substituted. Ambulation was permitted throughout treatment.

RESULTS

Within an hour and a half after injection of the solution containing hyaluronidase, the swellings were dramatically reduced in all cases and twenty-four hours later hematoma formation had diminished still further. In 3 patients, with severest symptoms, a second injection was administered in twenty-four hours with remarkable reduction of the swelling. All patients experienced definite subjective relief. No infection occurred.

The following is a typical case.

T. D., a 38 year old white man, had been attacked and beaten, and sustained a traumatic hematoma of the scrotum. The scrotum was enlarged to about three times normal size, with large areas of ecchymosis (fig. 1, *A*). It was tense, markedly tender and no areas of fluctuation could be found. There was some extension of swelling into the left inguinal region. Seventy-two hours after the injury hyaluronidase treatment was started. The area was prepared with zephiran chloride and a solution composed of 300 TR units hyaluronidase dissolved in 30 cc of saline, with 5 cc of 1 per cent procaine and 300,000 units of aqueous crystalline penicillin were injected into the left scrotum through the anterior surface. Pressure was applied for one hour with adhesive strapping, after which the swelling was slightly diminished and was definitely more resilient. The pain subsided. Twenty-four hours after injection the scrotal distention had been reduced by about one-third (fig. 1, *B*), and the patient was much more comfortable.

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* Wydase® (Lyophilized Hyaluronidase, N.N.R.) was supplied through the courtesy of Wyeth, Philadelphia. A TR (turbidity-reducing) unit is defined as the amount of hyaluronidase that will reduce the turbidity produced by 0.2 mg. of potassium hyaluronate in acidified horse serum to that produced by 0.1 mg. under assay conditions.

SUMMARY AND CONCLUSIONS

Hyaluronidase is of definite value in treatment of scrotal hematoma. Injection of hyaluronidase solution caused rapid resorption of the extravasated blood with remarkable alleviation of pain and discomfort in 7 patients with scrotal hematoma or hematocele. By causing early resolution of the swelling hyaluronidase probably reduces the liability to infection.

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ARGENTAFFIN TUMOR (CARCINOID) OCCURRING IN A BENIGN CYSTIC TERATOMA OF THE TESTICLE

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Benign cystic teratoma is the rarest tumor of the testicle, probably comprising less than 10 per cent of all teratomas. The tumor is congenital, benign, grows slowly and remains localized.[1, 2] Our purpose is to report the occurrence of a carcinoid tumor arising within a cystic teratoma of the testicle. A survey of the medical literature failed to disclose any previous report of this entity, although 5 cases have been reported in which the lesion occurred in ovarian teratomas. In 2 of these reported cases the carcinoid tumor appeared to arise in relation to intestinal epithelium,[3] in 1 case in relation to gastric mucosa,[4] in 1 case in association with respiratory-tract derivatives,[5] and in 1 case the tissue of origin could not be demonstrated.[6]

REPORT OF A CASE

A man, 58 years old, was first seen at the Mayo Clinic complaining of an enlarged left testicle. He said he had first noted this 14 years previously, and had been told by his physician that he had a hydrocele. Yearly physical examinations thereafter had demonstrated very slow progression of this enlargement. In the 2 years prior to his admission, however, he had noticed definite acceleration in the rate of enlargement, and he said that in this period he also had noted a definitely firmer consistency of the mass as compared to its former soft consistency. At no time had he suffered any discomfort or other symptoms.

Physical examination disclosed the left testicle to be approximately the size of a small orange. It could not be transilluminated, and was firm, not tender. Results of laboratory study were essentially negative: The erythrocyte sedimentation rate was normal, and results of serologic tests and of urinalysis were negative. A roentgenogram of the thorax disclosed nothing abnormal, as did a roentgenogram of the kidney-ureter-bladder area. An excretory urogram was reported as showing nothing of significance, although structural details were incomplete. A right pyelogram, made subsequently, also revealed nothing untoward. Trilobar enlargement (grade 1) of the prostate gland was found at

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* The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

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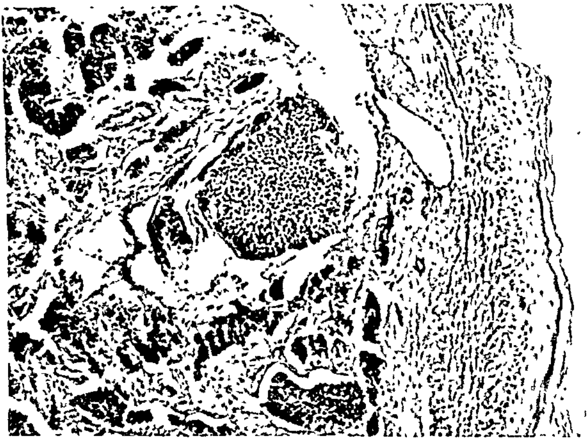

Fig. 1. Wall of cystic teratoma of testis. Cyst is lined by squamous epithelium and there is carcinoid tumor in wall consisting of groups of dark regular cells (hematoxylin and eosin, × 100).

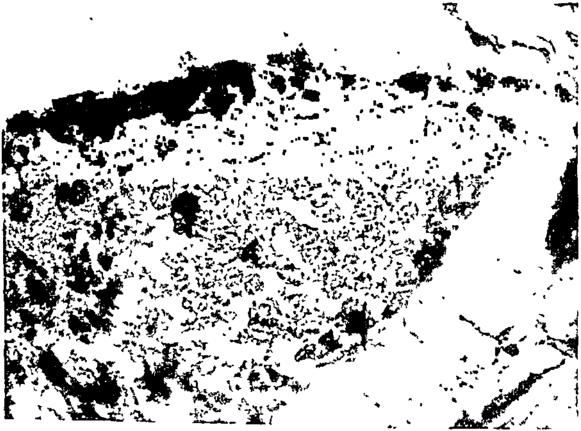

Fig. 2 Carcinoid tumor in cystic teratoma, showing argentaffin granules (Masson's silver method for argentaffin cells, × 550).

cystoscopy. There was no residual urine; Gram's staining of urine from the bladder demonstrated nothing of note.

The left testicle was removed by one of us (Culp) as follows: "The left scrotal contents were delivered through a low inguinal incision with a rubber-shod clamp on the spermatic cord. There was no fluid in the tunica vaginalis and the entire mass proved to be a diffusely enlarged testis. There was one firm area on the anterior surface. When a specimen was taken from this for biopsy, the scalpel entered a cavity from which exuded a large amount of milky fluid containing flaky material. The spermatic cord was then triply clamped, divided, ligated and transfixed with chromic catgut. The incision was closed with continuous catgut in the subcutaneous tissue and interrupted silk in the skin."

The patient's postoperative course was uneventful. The skin sutures were removed on the sixth postoperative day, and the patient was dismissed the following day.

PATHOLOGIC ASPECTS

Embedded in the testis was a cystic mass (5 cm. in diameter) filled with milky fluid containing flakes of whitish material. Lining the cyst was a whitish membrane. In the wall was a yellowish tumor (8 mm. in diameter).

Histologically, the cyst was lined by squamous epithelium. In the wall beneath the squamous epithelium were mucus-producing glands. The yellowish nodule was made up of cells which were very regular and were grouped into nests. There was a slight tendency toward acinar formation. The cytoplasm was pinkish and fairly voluminous; there were no mitotic figures (fig. 1). The silver stain demonstrated argentaffin granules (fig. 2).

The tissue in relation to which the carcinoid tumor arose could not be identified definitely, but appeared most closely to resemble respiratory-tract derivatives.

SUMMARY

What is believed to be the first reported case of a carcinoid tumor arising within a benign cystic teratoma of the testicle has been described in detail, both clinically and pathologically. The extreme rarity and benign nature of the lesion are emphasized.

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INTERSTITIAL CELL HYPERPLASIA IN ASSOCIATION WITH TESTICULAR TUMORS: A STUDY OF ITS RELATIONSHIP TO URINARY GONADOTROPHINS, TESTICULAR ATROPHY AND HISTOLOGICAL TYPE OF TUMOR

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Interstitial cell proliferation in association with germinal tumors of the testis has received scant attention and some investigators have even questioned its occurrence.[1] Dixon and Moore,[2] however, not only have demonstrated such hyperplasia but they have also indicated its unfavorable prognostic implication. These authors suggested a possible relationship between Leydig cell hyperplasia and biologically active tumor tissue but were unable to confirm this from their material. This is the report of a study which was undertaken to determine the incidence, etiology and significance of interstitial cell hyperplasia in association with malignant germinal tumors of the testis.

MATERIAL

The material for this study consisted of the clinical records, results of hormonal determinations and tissue sections of 36 patients who had germinal tumors of the testis. The patients were all between the ages of 19 and 32 years except for one man who was 41 years of age. Only patients whose urinary excretion of chorionic gonadotrophins† was determined were included. The excretion of pituitary gonadotrophins‡ (FSH) by all except 5 patients was determined. Unfortunately, only patients 28 and 35 had hormonal determinations prior to surgical removal of the primary tumor. The testes of the other men had been removed at other military hospitals prior to the patients transfer to St. Albans Naval Hospital. For the same reason, the number of tissue sections available was limited. Five patients were examined by autopsy.

OBSERVATIONS

The findings are summarized in table 1. Patients 6, 17 and 19 excreted chorionic gonadotrophins but the determinations were not quantitative. The number of slides listed in the table refers to the number of tissue sections of the primary tumor submitted with the patient.

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* Present address: Veterans Administration Hospital, Ann Arbor, Mich.

The opinions or assertions contained herein are the private ones of the author and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

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[1] Warren, S. and Olshausen, K. W.: Am. J. Path., 19: 307, 1943.

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† 24 hour rat ovarian hyperemia test.[3]

‡ 4 day immature mouse uterine weight test.[4]

Note: These hormonal determinations were performed by the Section on Clinical Endocrinology of the Sloan Kettering Institute of New York City.

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cystoscopy. There was no residual urine; Gram's staining of urine from the bladder demonstrated nothing of note.

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TABLE 2

FSH Excretion	Group I	Group II	Group III
Increased	1	6*	3
Normal	6	2	9
Decreased	1	1	2
Undetermined	2	2	1

Group I—Unequivocal interstitial cell hyperplasia.

Group II—Probable interstitial cell hyperplasia.

Group III—Absent hyperplasia.

* Three of these were associated with very high chorionic gonadotrophin levels and therefore may be "false" elevations (see text).

TABLE 3

Chorionic Gonadotrophin Excretion	Group I	Group II	Group III
Positive	6	5	0
Negative (no known tumor present)	2	5	6
Negative (tumor known to be present)	2	1	9

TABLE 4

Histological Tumor Components	Group I	Group II	Group III
Seminoma	5	3	5
Embryonal carcinoma	6	9	11
Adult teratoma	1	5	9
Choriocarcinoma	2	5	1

Leydig cells per microscopic field with the number found in nontumorous testes which exhibited similar tubular morphology.

Patients 1–10 of table 1 exhibited interstitial cells which were so numerous that the hyperplasia was unquestionable. These patients comprise group I of tables 2–4. Patients 11–21, group II, had probable hyperplasia. In most instances this equivocation was necessitated by the sparcity of the testicular parenchyma present in the tissue sections rather than by the actual number of Leydig cells present. Patients 22–36, group III, showed a normal or decreased number of interstitial cells.

Hyperplasia, when present, was diffuse although large focal aggregates were often encountered (fig. 1). When hyperplasia was present in the tumor-bearing testis it was also found in the opposite testis (patients 7 and 11). Areas immediately adjacent to tumor were found to be poorly representative inasmuch as they were often devoid of Leydig cells even though the latter were abundant in the parenchyma more distant from the tumor.

Other interstitial cell changes. Hypertrophy was a characteristic of most of the hyperplastic cells and was seldom seen in the absence of hyperplasia. The average diameter of the hypertrophic cells was about 20 microns (fig. 2, *C*). Atrophic Leydig cells were usually identified among the larger cells but were relatively

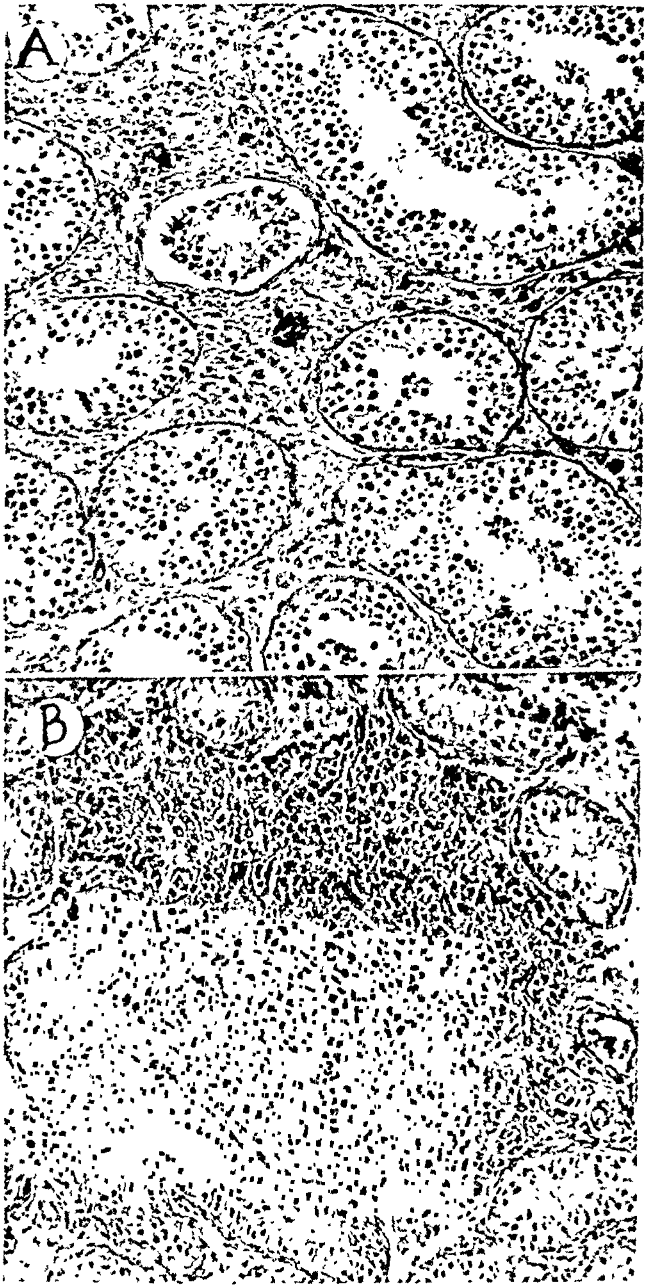

FIG. 1. *A*, interstitial cell hyperplasia in association with seminoma of testis. Note absence of tubular atrophy. Urine positive for chorionic gonadotrophins. *B*, marked focal hyperplasia of interstitial cells. Opposite testis contained embryonal carcinoma. Urine positive for over 104,000 I.U. chorionic gonadotrophins/24 hours.

less numerous than in testes which contained a normal or a decreased number of interstitial cells. There were exceptions to this, however, for in some instances the hyperplasia consisted largely of atrophic or degenerating cells (fig. 2, *A*). This was especially prominent in the tumor-free testes removed at autopsy in the case of patients who had hyperplasia in their surgically removed gonad and

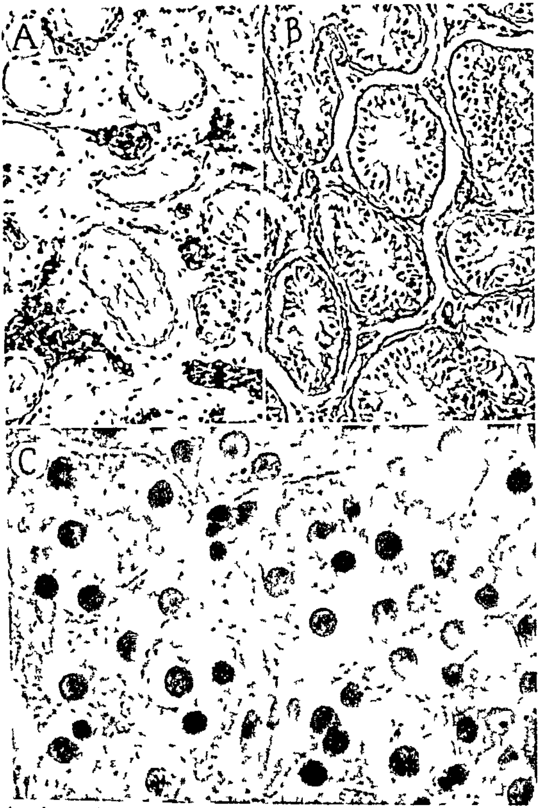

Fig 2 *A* advanced tubular atrophy Foci of atrophic hyperplastic interstitial cells Case of seminoma Urine positive for chorionic gonadotrophins *B*, seminiferous tubules lined only by Sertoli cells No interstitial cells seen Case of teratocarcinoma No chorionic gonadotrophins in urine *C*, hypertrophy of hyperplastic interstitial cells

who had received cytotoxic therapeutic agents or who were greatly debilitated It appeared probable that the number of atrophic cells increased with the duration of the hyperplasia but this could not be determined with certainty The atrophic change was characterized by decrease in cell size, distinct cellular borders, deep staining cytoplasm and small hyperchromatic or frankly pyknotic nuclei Another form of retrogressive change consisted of marked vacuolization and pale staining of the cytoplasm, indistinct cell borders, karyolysis and nuclear wrinkling Brown pigment granules (lipochrome) were generally more numerous in the hyperplastic cells than they were in the normal controls This pigment was especially prominent in the hyperplastic cells which had undergone atrophy

Seminiferous tubules. The seminiferous tubules exhibited retrogressive changes of varying degree. These changes, in order of increasing severity, consisted of: hypospermatogenesis, decrease in tubule size, thickening of basement membranes and disappearance of Sertoli cells (fig. 2, *B*). Although tubular atrophy was fairly ubiquitous, the lack of correlation between tubular atrophy and interstitial cell hyperplasia was readily apparent (table 1). Interstitial cell hyperplasia was often seen adjacent to normal appearing tubules (fig. 1, *A*) and many testes with markedly atrophic tubules failed to disclose even increased prominence, much less hyperplasia, of Leydig cells. Atrophy of the tubules was frequently unequal bilaterally, in contrast to the symmetrical interstitial cell hyperplasia.

Excretion of pituitary gonadotrophins (FSH). The urine of each of 31 patients was examined quantitatively for pituitary gonadotrophins (FSH) and in 10 of these the titer was elevated (52 mouse units/24 hours or above). There was no convincing correlation between FSH excretion and interstitial cell hyperplasia (table 2). In general, the testes of those patients who excreted excessive quantities of FSH disclosed greater tubular atrophy than did those of men who did not excrete excessive amounts of this hormone. The patients who had seminomas did not excrete more FSH than did the men with other types of testicular tumors. It should be mentioned at this point that it may be possible to obtain false positive biological reactions for FSH in patients who excrete exceptionally large quantities of chorionic gonadotrophins. This was found in the case of one patient who had an embryonal carcinoma and who was excreting over 104,000 I.U. of chorionic gonadotrophins per 24 hours. His urine also produced mice uterine changes which were indicative of increased FSH. Several weeks following a complete hypophysectomy (at autopsy no residual pituitary gland tissue was found) the "FSH" level was still elevated.

Excretion of chorionic gonadotrophins. Eleven patients excreted detectable amounts of chorionic gonadotrophins. Each of these also had interstitial cell hyperplasia (table 3). The testes of 10 of the 25 men who did not excrete chorionic gonadotrophins revealed Leydig cell hyperplasia but 7 of these 10 men had no demonstrable tumor at the time of the hormonal determinations. There did not appear to be a direct ratio between the level of hormone excretion and the degree of interstitial cell hyperplasia.

Histologic type of neoplasm. Attempts at correlation between Leydig cell hyperplasia and the histological type of neoplasm were complicated by the complex cytomorphology of most of the tumors. Therefore, each of the recognizable cytological components were listed (tables 1 and 4) rather than only the predominating component. It was readily apparent from the results in tables 1 and 4 that there was no correlation between histological tumor type and the presence of interstitial cell hyperplasia in this series with the notable exception of choriocarcinoma. Trophoblastic tissue was identified in 7 testes which showed interstitial cell hyperplasia and in only 1 testis which did not. The number which exhibited placental-like elements would undoubtedly have been materially increased had more tissue been examined.

DISCUSSION

It had been commonly believed that there was a direct relationship between atrophy of seminiferous tubules and hyperplasia of interstitial cells. This concept has been challenged recently.[1, 2, 5] The findings of this study strongly suggest that the number of Leydig cells is independent of the status of the tubules. Although it is true that interstitial cells are more conspicuous in the presence of tubular atrophy with resulting condensation of the stroma, the number of interstitial cells per microscopic field or per tubule is only slightly increased in comparison with those in testes which were regarded as showing hyperplasia. The additional features of Leydig cell hypertrophy and increased lipotrophic pigment within the hyperplastic cells were seldom encountered in testes which contained normal or decreased numbers of Leydig cells. The excessive quantity of lipochrome pigment granules apparently bears the same relation to Leydig cell hypertrophy as does the paranuclear lipofuscin pigment of myocardial fibers.

Other findings supported the impression that there was no correlation between interstitial cell hyperplasia and tubular atrophy. Striking increase in Leydig cells was occasionally noted in association with normal appearing tubules and Leydig cell hyperplasia, when present, was bilateral, while tubular atrophy exhibited no such symmetry. Atrophic tubular changes were common in the tumor-bearing testis because of compression or invasion by neoplastic tissue. Atrophy of the tumor-free testis was probably the result of cachexia or the use of cytotoxic therapeutic agents.

It is apparent, therefore, that the Leydig cell change is not the result of tubular atrophy. The only other feasible explanation rests with the hormonal hypothesis. Interstitial cell hyperplasia has been produced in experimental animals by the administration of many diverse agents, including pituitary gland extracts, chorionic gonadotrophins and estrogens.[1, 6, 7] It is reasonable to assume that interstitial cell hyperplasia in association with germinal tumors of the testis could be the result of stimulation by the hypophysis or by biologically active neoplastic tissue.

This study disclosed no definite relationship between the excretion of pituitary gonadotrophins (FSH) and interstitial cell hyperplasia. Dixon and Moore suggested that interstitial cell hyperplasia could be the result of the elaboration of hormones by the neoplastic tissue and this study bears out the correctness of their hypothesis. Proliferation and hypertrophy of Leydig cells correlated well with urinary excretion of chorionic gonadotrophins and it appears that the hyperplasia is produced by the elaboration of hormones by biologically active tumor tissue in the primary or metastatic lesions. Twombly[6] has stated that tumors which elaborate large quantities of chorionic gonadotrophins also seem to pro-

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[5] Sniffen, R. C., Howard, R. P. and Simmons, F. A.: A. M. A. Arch. Path., 51: 293, 1951.

[6] Twombly, G. H. and Pack, G. T.: Endocrinology of Neoplastic Disease. Oxford University Press, 1947, p. 288.

[7] Cameron, A. T.: Recent Advances in Endocrinology. Philadelphia: The Blakiston Co., 1947, 6th ed., p. 240.

duce estrogens. Inasmuch as both estrogenic substances and chorionic hormones can produce interstitial cell proliferation in experimental animals, and probably in man, it remains to be determined which of these two substances is the active etiological agent. More significant, from a practical standpoint, is the fact that Leydig cell hyperplasia in association with testicular tumors frequently indicates the presence of biologically active trophoblastic tissue. Such tissue was found histologically in only 7 of the 21 testes which showed hyperplasia but the inadequacy of the amount of tissue sampled has already been emphasized.

Every testis with a malignant tumor should be examined for the presence of interstitial cell hyperplasia and when the latter is present, a vigorous search should be made to discover trophoblastic elements in the tumor, especially if there are no facilities for the determination of chorionic gonadotrophin excretion. Conversely, if no interstitial cell hyperplasia is noted, it is very unlikely that the patient's urine will reveal chorionic hormones. An advantage of the study of the interstitial cells is that hyperplasia, when present, is diffuse and will be present in any of the sections which contain nontumorous testicular parenchyma, unlike the trophoblastic tissue which is frequently very focal or occasionally difficult to recognize.

In view of the close association between interstitial cell hyperplasia and the elaboration of chorionic gonadotrophins (and therefore choriocarcinoma) it is not surprising that Dixon and Moore[2] found that the two year mortality of men with testicular tumors was more than doubled when interstitial cell hyperplasia was found and that this increase was sixfold in their seminoma group.

The practice of ascribing chorionic gonadotrophin production to such tumors as adult teratomas or seminomas has led to confusion.The fact that such tumors must also possess chorionic tissue and therefore are, in part, choriocarcinomas despite failure to demonstrate such components histologically, had been ignored frequently. The impracticality of examination of testicular tumors by serial sections to find all the various histological components and the acknowledged clinical significance of the presence of biologically active tumor tissue lend support to the arguments of those who recommend a classification of testicular tumors which is based upon a combination of histology and hormonal production.[8]

Although there proved to be no definite relationship between excretion of FSH and interstitial cell hyperplasia, it is of interest that over 30 per cent of those tested showed an increased excretion of this hormone. It is normally excreted in small quantities and has been referred to as the "castrate" hormone because it is excreted in excessive amounts in elderly men, menopausal women and castrates. It has been shown that increased output is accompanied by a decreased output of male sex hormone[6] and Howard et al.[9] have demonstrated a direct relationship between increased FSH excretion and testicular atrophy. Brewer[10] clearly summed up this relationship when he stated "increased excretion of FSH does not indicate the presence of biologically active tumor tissue and probably indicates the presence of reduced testicular function." It has been claimed that patients with seminoma frequently excrete excessive FSH but no such correlation was found in this study. As a matter of fact, none of the men with "pure" seminomas had elevated FSH levels.

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[8] Powell, T.: J. Urol., **39**: 522, 1948.

[9] Howard, R. P., Sniffen, R. C., Simmons, F. A. and Albright, F.: J. Clin. Investig., **10**: 121, 1950.

[10] Brewer, J. I.: Arch. Path., **41**: 480, 1946.

CONCLUSIONS

Interstitial cell hyperplasia is frequently found in association with germinal tumors of the testis.

There appears to be a close correlation between interstitial cell hyperplasia and the excretion of chorionic gonadotrophins.

There is no significant relationship between interstitial cell hyperplasia and tubular atrophy or urinary excretion of FSH.

The author wishes to express his appreciation to Dr. F. K. Mostofi for his criticism and suggestions.

The photomicrographs were taken by Mr. Mort Russin.

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ADENOCARCINOMA OF THE EXCRETORY DUCTS OF THE TESTICLE

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Adenocarcinoma arising in the excretory ducts of the testicle has received scant recognition in the literature, and most authorities do not mention it when reviewing malignant disease of that organ. Willis (1953) emphasizes the importance of careful study of the different parts of an epithelial testicular tumor in order to distinguish it from a teratoma of predominantly glandular structure. Three cases of adenocarcinoma occurring in a scrotal testicle have previously been recorded (Scully and Parham, 1948; Badenoch and Dukes, 1951; Shilltoe, 1952); while Dundon (1952), working in this clinic, reported one following orchiopexy. An adenocarcinoma does not appear however to have been described before in a maldescended testicle.

CASE REPORT

R. W., aged 21 years, was referred with a right maldescended testicle, associated with an aching pain in the groin after exercise. Two years previously he had been turned down for National Service on account of the anomaly. He stated confidently that the testicle had not increased in size during the past two years.

There was a well-formed left scrotal testicle, the right side of the scrotum being empty. Lying just lateral to the right external ring and outside the external oblique aponeurosis was a swelling, 5 by 4 cm. In shape it resembled a testicle, but was firmer than a normal organ. It was slightly tender; abdominal palpation did not reveal any abnormality.

This patient had an obvious right maldescended testicle. In a man of his age, one would have expected an ectopic testicle to be soft and atrophic, and not of the size and consistency of a well-formed, normal scrotal one. It was therefore felt that malignant degeneration could not be excluded and orchiectomy was advised. Before operation a Hogben test was done. This proved to be negative, while a chest x-ray showed the lung fields to be clear.

The testicle was exposed through the usual inguinal incision. Care was taken to open the canal lateral to the testicle in order to isolate and divide the cord before manipulating the organ itself.

The patient was referred to the radiotherapist, Dr. R. Gibb, of the Christie Hospital, Manchester. Despite the somewhat unusual histological report he advised that a course of postoperative radiotherapy should be carried out.

Pathological report (Dr. A. A. Miller): The specimen consisted of the testis with epididymis which had been incised revealing an ovoid, lobulated tumor measuring 6 by 6 by 3 cm. In most aspects it was surrounded by a compressed layer of testicular epithelium: parallel slices of the tumor revealed a polycystic growth with large areas of solid white and partly friable necrotic material. The

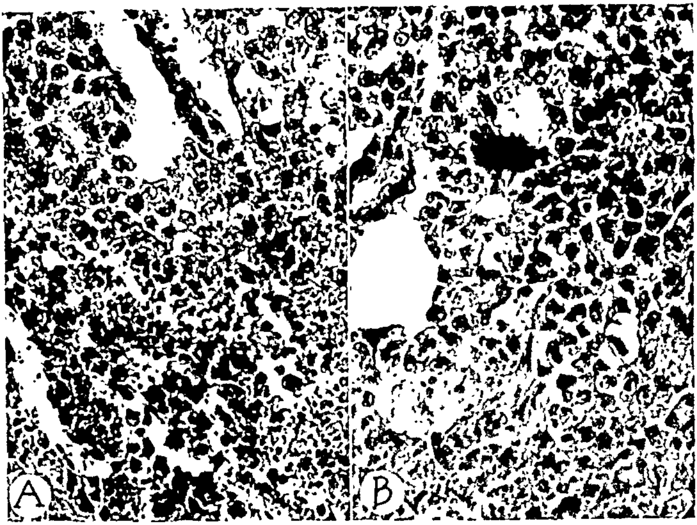

FIG. 1. *A*, photomicrograph of testicular tumor showing adenocarcinoma. *B*, another microscopic field showing solid carcinoma with feeble acinar structure.

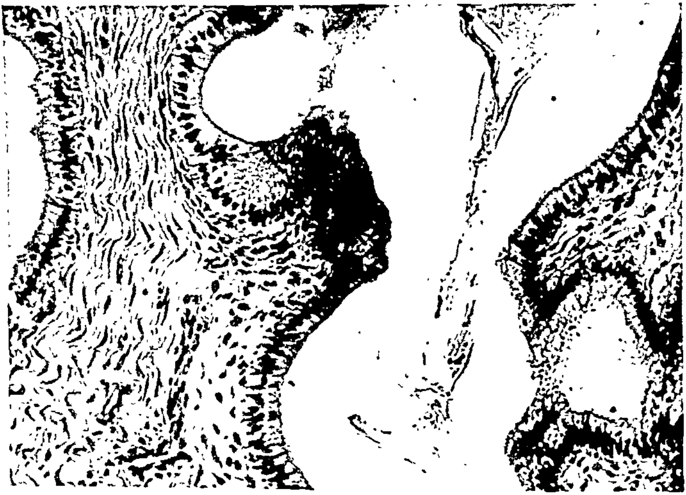

FIG. 2. Photomicrograph of epididymis showing cyst and glands lined by mucus-secreting goblet cells.

of the epididymis and the mediastinum testis were cystic, the cysts con-
g pale green gelatinous material.
roscopic examination of ten blocks from different parts of the growth
d a malignant testicular tumor with the structure of a disorderly papil-
denocarcinoma (fig. 1, *A*); the acinar arrangement was feeble in places
, *B*), and there were large areas of anaplasia and necrosis. An unusual fea-
n the epididymis was the presence of cysts and glands lined by mucus-
ng goblet cells which suggested metaplastic change or teratomatous ele-
(fig. 2). An extensive search in other parts of the neoplasm did not reveal
ture of cartilagenous mesenchyme and squamous epithelium to support a
matous origin and there were no areas of seminomatous tissue. While the
t's age, together with the epithelial nature of the growth suggested a tera-
the structure and staining properties of the tumor tubules closely resem-
ose of the straight or rete tubules: and it was concluded that this was the
le *origin of the adenocarcinoma.*

COMMENTARY

classification of testicular neoplasms is still in a somewhat confused state,
doubt to the various observers using different terminology for the same
r. Willis (1948) gives the following classification:
eminoma, arising from the cells lining the seminiferous tubules.
eratoma, a tumor containing a variety of tissues unlike those of the nor-
stis.
nterstitial cell tumors, often associated with precocious puberty.
denocarcinoma of the excretory ducts of the testicle. This last tumor may
ratesticular, arising from either the straight, the rete or the efferent tubules,
ratesticular, arising from the epididymis or ductus deferens. Whitehead
Villiams (1951) have recently reported an example of the latter.

liability to neoplastic change is said to be fifty times greater in an ectopic
e as compared to a normal scrotal one (Gilbert and Hamilton, 1940).
ver, an otherwise successful orchiopexy does not wholly protect against
ndency, as in the case reported by Dundon (1952), an adenocarcinoma oc-
l 10 years after orchiopexy.

s well recognized that all cases of maldescended testicle occurring in an
with a well-formed contralateral scrotal testicle should be submitted with-
lay to orchiectomy. Moreover, all such testicles should be sent for patho-
l examination. In the present case there was only a suspicion on clinical
nation that the testicle might be malignant, and it was only on receipt of
thological report that the true nature of the case was appreciated and sub-
nt treatment of the possible metastases instituted.

radical extraperitoneal operation for malignant testicular neoplasm (Hin-
1923) is no longer advocated in this country, although it is still popular in
ca, where more extensive techniques are still being described (Lewis,
. It is generally agreed that simple orchiectomy combined with postopera-
diotherapy is the treatment of choice. The inguinal incision, used for her-

morrhaphy, is preferable. By using this incision, the cord can be isolated and divided at the internal ring as a first step, before the actual malignant testicle is mobilized, thereby preventing tumor emboli from being squeezed into the lymphatic or venous circulations.

The scrotal incision, which serves so well for other operations on the testicle such as hydrocoelectomy, epididymectomy, etc., should be avoided. This incision, even when apparently well healed clinically, breaks down under radiotherapy. The combination of serous discharge and x-rays causes a very marked scrotal reaction, which causes the patient extreme discomfort (Gibb 1953). It is *nowadays considered essential to radiate the scrotum as well as the abdomen,* inguinal regions and pelvis. In a young man without a family, an attempt is made to screen the remaining testicle, but if the patient already has a family, no such attempt is made. Recurrence in the scrotum is, of course, not unknown.

SUMMARY

An adenocarcinoma arising in the excretory ducts of a maldescended testicle is described. A plea is made for histological examination of all excised ectopic testicles. A hitherto unsuspected neoplasm may thereby be disclosed.

I wish to thank Mr. W. H. Graham, F.R.C.S., for permission to publish this case, and also Dr. A. A. Miller, M.D., for the pathological report and photographs.

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HEMANGIOMA OF TESTIS AND EPIDIDYMIS

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Hemangioma of the testicle is a rare tumor. Despite the frequent occurrence of this tumor in other parts of the body, only 4 cases of hemangioma of the testicle have been reported.

The first case was recorded by Muto[1] in 1927. A 2 year old child had a mass in the scrotum and another in the chest. The mass in the scrotum was resected and found to be a hemangioma of the testicle. Later, resection of the chest mass was attempted, with death of the child. The diagnosis of the chest mass was lymphangioma.

In 1944 Moorehead and Thomas[2] reported the case of a 75 year old man with a history of 6 months painful enlargement of the right testicle. It was enlarged, firm and tender. The testicle was resected. It was completely replaced by firm tissue so that no distinction could be made between the epididymis and testis. The mass measured 8 by 6.5 by 4 cm. The diagnosis was cavernous hemangioma of testicle, probably originating from the tunica vasculosa.

The same year A. H. Kleinman[3] reported the case of a 61 year old man with painless progressive enlargement of the left scrotal contents, of 1 year's duration. The testicle appeared two to three times normal size. It was firm, smooth and nontender. Radiation was given, totaling 5300 r., followed 3 weeks later by orchiectomy. Grossly the left testicle was only slightly larger than the right testicle. The tunica vaginalis was thickened. A dark red nodule measuring 2 cm. in diameter was noted in the center of the testicle. The microscopic diagnosis was hemangioma cavernosum.

The most recent case was reported by A. A. Rosenthal[4] in 1946. An infant 3 months old had had a hydrocele since birth. There was no history of injury. The hydrocele, which was transilluminated, was aspirated at intervals with recurrence. Because of intractability of the hydrocele, and the danger of infection or trauma to the testis from repeated aspiration, operation was advised. When the tunica vaginalis was opened, the testis was bluish black in appearance but not enlarged. It was thought to be gangrenous as a result of repeated trauma from the aspirations, and, therefore, was resected. The specimen was an oval, smooth, dark bluish-gray mass of tissue including the testis, epididymis and wall of hydrocele sac. The testis and epididymis on section were dark bluish-gray. The microscopic diagnosis was vascular and cavernous hemangioma of testis and epididymis; hydrocele of the tunica vaginalis.

Because of the rarity of this tumor, we thought a case encountered recently in this hospital should be reported.

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[1] Muto, M.: Mitt. u. Allg. Path. u. path. Anat. Tokyo, 4: 142, 1927.
[2] Moorehead, R. P. and Thomas, W. C.: J. Urol., 51: 72, 1944.
[3] Kleinman, A. H.: J. Urol., 51: 548, 1944.
[4] Rosenthal, A.: J. Urol., 55: 542–544, 1946.

CASE REPORT

E. G., a 15 year old white boy, was admitted to the Albert Einstein Medical Center, Northern Division, on August 10, 1951 with a chief complaint of pressure sensation in the scrotum. Five days before admission he was awakened by pain in the right side of the scrotum and felt a mass in this area. The pain subsided following a hot bath but later recurred. In August 1950 he had had a tender mass in the same region. The mass subsided after 24 hours.

The past history was negative except for a right inguinal hernia which followed whooping cough at 3 years of age. He wore a truss for several years. There was no definite history of trauma, although the patient was active in sports.

The physical examination was essentially negative except for a hard, slightly tender mass measuring about 8 cm., in diameter, noted in the right scrotum. It was freely movable and did not transilluminate. There was no hernia or inguinal lymphadenopathy.

Laboratory findings: Red blood cells 4,800,000 with 14.4 gm. hemoglobin. White blood cells 12,750 with a differential of 70 per cent polymorphonuclears, 27 per cent lymphocytes, 3 per cent monocytes. Urine negative.

The admission diagnosis was torsion of the testicle. At operation, the testicle was enlarged and surrounded by a hematoma which appeared to lie between the tunica vaginalis and the tunica albuginea. No abnormality of the spermatic cord was noted. There was no evidence of a hernia. The testicle was thought to be gangrenous and was resected. The postoperative course was uneventful.

Macroscopic: The specimen consisted of a testis, epididymis, and cord structures. The tunica vaginalis was thickened. The testis measured 4.5 by 3.5 by

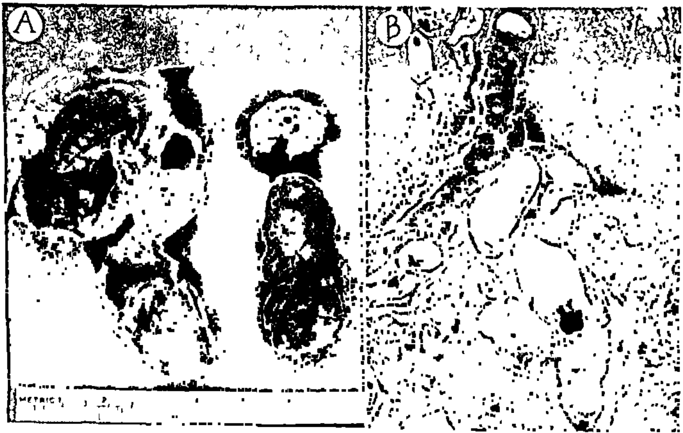

FIG. 1. *A*, testis, epididymis and cord sectioned to show hemorrhage and spongy tumor. *B*, microscopic section showing cavernous hemangioma. Tubules of epididymis are seen at upper right.

0.7 cm. It was bluish-black and softer than normal. The tunica albuginea was also thickened. On section, only a small rim of testicular tissue was seen near the upper pole. The remainder of the testis was replaced by old blood. No tumor was recognized. The epididymis was also hemorrhagic. The spermatic vessels were thrombosed (fig. 1, *A*).

Microscopic: Sections of the testis showed a small area of degenerated tubules, surrounded by blood. Most of the sections showed complete replacement of the tubules by numerous endothelium-lined spaces which varied widely in size and shape but for the most part were small and oval. The intervening stroma was composed of fairly dense fibroconnective tissue. The epididymis was also partly replaced by many endothelium-lined spaces. Many sections were examined and no evidence of teratoma was found. The diagnosis was hemangioma, involving testis and epididymis (fig. 1, *B*).

DISCUSSION

Benign tumors of the testis are infrequent and constitute only from 2 to 4 per cent of all neoplasms of the testis.[5] The least frequent benign tumor is the hemangioma. Despite the fact that this tumor has been described, from time to time, involving the epididymis, cord, scrotum and even tunica vaginalis, scant reference is made to hemangioma of the testis. It is not mentioned in the Henke-Lubarsch.[6] In a personal communication, Dr. Mostofi stated that two cases are in the files at the Armed Forces Institute of Pathology. One was an incidental finding in a newborn infant, dead of other causes; the other was in a man of 25 years of age who had a mass in the left scrotum, presumably separate from the testis.

Hemangioma may occur at any age. Because most testicular tumors are malignant, and the difficulty of differentiating clinically a benign from a malignant one, all testicular masses should be explored and treated as the process indicates. This case, and that of Rosenthal, indicate the possibility of clinically confusing hemangioma and hemorrhagic infarction of testicle. Before exploration, hormone studies are advisable.

SUMMARY

The fifth reported case of hemangioma of the testicle is described. These tumors may occur at any age. Their importance lies in the fact that they must be differentiated from malignant tumors where the prognosis is much different. Clinically, it is difficult to differentiate between a malignant and a benign tumor of the testis and, therefore, exploration is necessary.

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SOME OBSERVATIONS ON THE SEMINAL DUCTS

HARRY C. ROLNICK

I am highly honored in having been chosen as the Belfield lecturer for this year. I have wanted for many years to pay my tribute to William T. Belfield and am happy the opportunity has been afforded me. No previous essayist has spoken of the seminal duct which was his chief interest and with which his name is so closely associated. Belfield's clinical and experimental observations on the seminal duct and his careful and lucid writings have left their imprint on this subject and it is appropriate, therefore, to review at this time some of our knowledge in this field.

Belfield's concept of the analogy of the seminal duct to the urinary tract, while of considerable interest and true in part, cannot be entirely substantiated. His concept was that the seminal duct is analogous to the urinary tract both embryologically and physiologically. Thus, the epididymis is the analogue of the kidney, the tail of the epididymis the analogue of the renal pelvis, the vas deferens the analogue of the ureter, the seminal vesicle analogous to the urinary bladder and the ejaculatory duct analogous to the prostatic urethra.

THE SEMEN

The semen is a highly alkaline secretion which can be compared with blood. Its alkalinity is greater than that of blood. The pH of seminal fluid ranges from 7.05 to 7.41 and its proteins consist of proteoses and globulins. The spermatozoa are produced in the testis and the plasma of the semen in the accessory sex organs. Considerable fibrinogen and thromboplastin are present in the semen, and the process of coagulation and liquefaction of semen by them resembles somewhat the actions of the same substances present in the blood. Fibrinolysin is found in the prostatic secretion and when applied experimentally to blood, delays blood coagulation.[1] Fructose and citric acid are the important chemicals present in normal semen. Hyalouronidase is produced by the testis only and there is apparently a definite interrelationship of the spermatozoa count, hyalouronidase and the possibility of fertilization.[2] The presence or absence of hyalouronidase in the semen is an additional indicator of testicular function or obstruction in the seminal duct.[3] Thus in azospermia, absence of hyalouronidase indicates obstruction in the epididymis or vas and its presence in azospermia indicates that the ducts are not blocked.

The spermatozoa are nonmotile at their site of origin in the testis. They are nonmotile in the epididymis, although occasionally some motility is noted in the tail of the epididymis. They are nonmotile in the vas deferens but evidence motility in the ampulla of the vas and in the seminal vesicles.

The spermatozoa form only a small part of the semen. Most of the ejaculated

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The twenty-fifth annual William T. Belfield Memorial Lecture presented before the Chicago Urological Society October 26, 1953.

[1] Huggins, Charles and Neal, William: J. Exp. Med., **76**: 527–542, 1942.

[2] Sallman, Bennett and Birkeland, J. F.: Am. J. Physiol., **152**: 271–279, 1948.

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semen consists of secretion from the accessory glands. The high alkalinity and viscid nature of the semen is also derived from the accessory glands. The maturation of the spermatozoa is probably not completed until they have passed through the epididymis and entered the ductus deferens. The medium of nourishment and the sustaining of optimum sperm life after ejaculation is due to the secretions from the seminal vesicles, prostate and the bulbo-urethral glands. The epididymis, prostate, seminal vesicles and the bulbo-urethral glands are the accessory sex organs which elaborate the seminal plasma.[4] Fructose and citric acid are the most important constituents of the plasma, which is the nutrient for the spermatozoa. Production of the seminal plasma is subject to strict control by various hormones, particularly the testis,[5] and the pituitary. Castration produces atrophy of the prostate and seminal vesicles and administration in these castrates of testosterone causes return to normal of these structures. Both fructose and citric acid, which are the most important chemicals necessary for the metabolism of the spermatozoa, disappear from the seminal plasma after castration and reappear promptly after administration of testosterone. The presence or absence of fructose and citric acid in the semen is an indicator of hormonal function of the testis. The composition of seminal plasma, unlike any other body fluid, is subject to considerable variation even in the same animal. There is some seasonal variation of fertility in the human; some statistics have shown that April is the month of highest fertility.[6] Most of the sperm are in the first part of the ejaculate and the motility of the spermatozoa is poorest in the last portion of the ejaculate.

The spermatozoa are nonmotile at the site of their origin in the testis and in the epididymis because they have no fructose at their disposal and there is practically no fructose present until the spermatozoa reach the ampulla and seminal vesicles. The seminal vesicles are the chief contributors of fructose and spermatozoa utilize this fructose for their metabolism and for their activity. The survival of spermatozoa in ejaculated semen depends largely on the amount of fructose present. A low semen fructose level suggests either hormonal or spermatozoal deficiency; however a high level of semen fructose does not necessarily indicate great spermatozoal efficiency for a high level is often found in diabetes. The end product of the metabolism of fructose is lactic acid.

Surgical obstruction of the vas deferens or congenital absence of the vas or epididymis does not cause degeneration of the testis. The testis continues to secrete and produce spermatozoa, although this activity is markedly reduced, even though the epididymis or vas is completely obstructed. Spermatogenesis is present also even in congenital absence of the vas deferens. The restoration of the continuity of the vas deferens after it has been resected results in return back to normal within 6–12 months of the secretion of the testis. Moore demonstrated spermatogenesis in congenital absence of the vas. We have observed this in one patient who had complete azospermia and in whom we found spermatogenesis on testicular biopsy. This patient was later operated upon for the relief of possible obstruction in the epididymis or vas, at which time congenital absence of the tail of the epididymis and vas deferens was noted.

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Anomalies of the seminal duct are probably as frequent as those of the urinary tract. I have noted at necropsy complete absence of the seminal vesicles. The seminal vesicles may be rudimentary, the ejaculatory duct may be absent on one side. We have also seen complete separation of the body and tail of the epididymis.

THE EPIDIDYMIS

The epididymis is a single tubule formed by the junction of the vasa efferentia emanating from the rete testis. It is very much coiled and twisted upon itself and if unwound would be 20 feet long. The epithelium of the epididymis is not ciliated. It has projecting ends which dip into the lumen and elaborate the secretion which can readily be found in the lumen of the epididymis. The spermatozoa which are nonmotile in the epididymis are carried along to the vas deferens by secretory pressure and by contractions of the muscle fibres in the fascia of the epididymis.

The epididymis is a derivative of the wolffian body. It is the passageway for spermatozoa from the testis and continues as the vas deferens. It also has a secretory function. These two functions are well recognized. Some years ago we attempted to determine whether the epididymis has an excretory function similar to the kidney. We found dye in the body of the epididymis following the injection intravenously in the dog of high concentrations of mercurochrome, methylene blue and indigo carmine. However, this has not been verified by others and repeated observations by me have brought varying results, some positive and others negative. The epididymis as a separate structure for the passage of spermatozoa is present in all species higher than the amphibian and is a well developed structure in the mammal. It would seem that it must have a definite purpose other than merely being a passageway for the spermatozoa. Belfield's statement was to the effect that it would be odd for a spermatozoan $\frac{1}{500}$ of an inch long to travel 20 feet, 100,000 times its own length in order to get anywhere if there were not some purpose in this. The function of the epididymis in relation to the spermatozoan is as yet not clear. It has been postulated by many that the secretion of the epididymis acts toward maturation of the sperm. This is probably true but has not been definitely proven. A study by Weisman[7] on spermatocele fluid presents the finding that most of the spermatozoa in a spermatocele cyst are immature and he concluded that epididymal secretion is necessary for maturation of the spermatozoa and that the maturation of the sperm is not completed until they enter the ductus deferens. Spermatocele cysts are nearly always found at the head of the epididymis. I have found in examining spermatocele fluid that although some of the spermatozoa are motile they are smaller than normal and their life duration on the slide usually very short. The alkalinity of the fluid in a spermatocele cyst is less than in ejaculated semen.

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[7] Weisman, A. I.: J. Urol., 46: 423–426, 1941.

The spermatozoa constitute only 10 per cent of the semen, the rest or 90 per cent consists of plasma. Belfield's concept was that most of the secretion composing the human semen is produced by the epididymis. He based his conclusions on the clinical observation that in obstructive sterility in the male following epididymitis or resection of the vas that the ejaculate is only about ⅙ of what it had previously been. Therefore, since only the spermatozoa and the epididymal secretion are absent under these conditions, he concluded that most of the secretion of the semen was the product of the epididymis. However, Huggins and Scott[8] state that ligation of the vas deferens does not appreciably change the quality or quantity of the secretion of the semen and that the plasma of the semen is largely the secretion of the prostate and seminal vesicles. Here is a field, the function of the epididymis, which is still open for study.

SPERMATOCELE

Spermatocele cysts are usually found at the head of the epididymis and are extravaginal in the vast majority of cases. They are common and are often mistaken for hydrocele. Some of the unsuccessful results in hydrocele operations are due to the fact that a spermatocele was present and overlooked. Spermatoceles require resection and not a so-called "bottle" operation. When one dissects the cyst very carefully it will be found that it originates either in the head of the epididymis or the rete testis. Occasionally one can dissect a spermatocele cyst completely and find that its true nature is that of an aberrant duct ending blindly, originating either from the rete testis or the epididymis. The spermatocele cyst in the vast majority of cases is the result of the dilatation of the blind end of a vas efferens which has not united with the other vasa efferentia to form the head of the epididymis. The blind end of this aberrant duct begins to dilate when the individual becomes mature, due to its filling up with spermatozoa. As the result of the secretory pressure it gradually dilates similar to a rubber balloon when it is distended and thus a cyst of varying size is gradually formed. The appearance of the fluid in a spermatocele cyst is either pale grey, or soapy depending chiefly upon the quantity of spermatozoa present. Of interest here is the observation by Weisman and numerous observations by myself that while one can find some live sperm in the spermatocele fluid most of the sperm are dead or appear immature. If the epididymis is necessary for the maturation of sperm then attempts to inseminate the female by spermatozoa aspirated from the testis have no scientific basis. Neither does short-circuiting of the vas to the spermatocele cyst have much value if this is true. The various operations for short-circuiting the vas in the presence of obstruction in the tail of the epididymis by either uniting the vas directly to the testis or to the head of the epididymis probably have very little merit for the sperm have not traveled through the epididymis and have not had an opportunity to mature.

THE VAS DEFERENS

This structure is analogous to the ureter for it is the original wolffian duct. It is an elastic structure which can be drawn far out of its sheath in the scrotal

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[8] Huggins, Charles and Scott, W. W.: Am. J. Physiol., **136**: 467–473, 1941.

vas It has a thick wall of longitudinal muscle fibres but no circular fibers and a narrow lumen It winds its way about forming a loop and travels through the pelvis, crossing the ureter, and finally ends in the ampulla, its dilated portion Although contractions of the vas occur these do not produce the same peristaltic waves as in the ureter for the vas deferens has no circular muscle fibers The spermatozoa pass down the vas deferens to the seminal vesicles and ampulla chiefly by secretory pressure They are also aided by the muscular contractions of the vas which are greatly increased during coitus Fructose, the vital carbohydrate necessary for sperm metabolism, is not present in the vas and therefore the spermatozoa are still nonmotile However, motility of the sperm is noted in the ampulla of the vas The ampulla is often well developed and quite large and can be a receptacle for the spermatozoa until they are expelled by the involuntary contractions of its smooth muscles as in the case of the seminal vesicle or at ejaculation Studies by Waddell[9] show that the vas has sympathetic and parasympathetic innervation and that its ability to undergo contractions is also inherent in the muscle itself The vas, as well as the ureter, is affected by certain drugs Waddell has shown that the vas has muscular contractions of its fibers and that this can be affected by various drugs such as strychnine, quinine and cocaine through their direct stimulation of the muscle fibres and not necessarily by action on the nerves Studies by Macht on the physiology of the ureter and vas deferens reported some years ago are still of interest The ureter has great vitality and can undergo contractions for a long time in suitable medium The vas deferens in suspension preparation under suitable conditions shows rhythmic contractions but these movements are not so constant or so easily obtained as in the ureter[10] Only longitudinal segments of the vas deferens showed movements and not complete rings or portions of the vas deferens as in the case of the ureter This is due to the fact that the vas deferens has no circular fibers Suitable solutions for activity of rings or segments of the ureter are Ringer's or Locke's with the addition of sodium chloride and an acid medium The vas undergoes activity best in Tyrode solution with the addition of sodium bicarbonate which is an alkaline medium This is the normal medium for seminal plasma which is alkaline, whereas urine is acid in higher mammals The vas has sympathetic and parasympathetic innervation which responds to the action of various drugs A rise in temperature first stimulates and subsequently paralyses the movements of the vas and ureter A fall in temperature inhibits ureteral and vas contractions

REGENERATION OF THE VAS DEFERENS

It has been recognized clinically for many years that attempts at sterilization of man by either cutting or tying the vas are often unsuccessful I demonstrated many years ago that the vas deferens regenerates very rapidly after it has been cut or tied and that this regeneration is aided by its sheath Therefore if vasectomy is to be properly done, a rather large portion of the vas should be resected and the cut ends crushed and turned backward Successful re-anastomosis of the vas deferens is possible many years after resection. The remarkable regenerative capacity of all epithelial-lined ducts is exemplified here as well as in other portions of the body and it is chiefly this regenerative capacity that makes urologic surgery possible.

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[9] Waddell, J A J Pharmacol , 9 279-286, 1917

[10] Macht, D I J Urol , 1: 97-111, 1917

THE SEMINAL VESICLES

Ever since the days of Fallopius hundreds of years ago there has been a dispute as to the function of the seminal vesicles.[11] Fallopius and others maintained they are the reservoir or storehouse for the spermatozoa. Swammerdam and Hunter disputed this and were of the opinion that they merely act to secrete a portion of the seminal plasma. The anatomy of the seminal vesicles was not well understood until radiography of these structures had been done. Picker first showed the seminal vesicles on x-ray and Belfield later made many of his original observations through radiography of the seminal vesicles. Belfield stated that the seminal vesicles in the human are structures peculiar to the human and the anthropoid ape. They are hollow structures with a twisted tubule like a pea in the pod. In the lower species of mammals they are only glandular structures and not vesiculae seminales but glanduli seminales. He contended that the seminal vesicles in the human are true reservoirs for semen and that they are analogous to the urinary bladder which is the reservoir for urine. He based his conclusion on the observation that fluid injected through the vas fills the seminal vesicle before overflowing through the ejaculatory duct into the prostatic urethra and the bladder. He concluded that the spermatozoa enter the seminal vesicle and remain there until expelled. The sphincters at the neck of the seminal vesicle and about the ampulla allow the seminal vesicles to retain their contents, except when peristalsis of the vesicles occurs. The seminal vesicles do not, however, retain all their contents until ejaculation occurs, but contract at intervals expelling their secretions. The mechanism here is similar to that of other hollow organs containing smooth muscle, involuntary contractions occurring in a manner similar to that of the gallbladder. Belfield first demonstrated that the urine in most men contains a few spermatozoa at various times; in fact about 25 per cent of all urine specimens in the adult male contain spermatozoa. The contraction of the seminal vesicles may be due to the smooth muscle in its wall, or the vesicle may be considered as merely a receptacle similar to the gallbladder which distends and empties. The contraction of the elevator ani, however, is also an important factor in expelling the contents of the seminal vesicles. Thus terminal phosphaturia which is occasionally observed is due to the sudden expulsion of the contents of the seminal vesicles by the contraction of the perineal muscles.

VESICULAR ALBUMINURIA

The proteins of the semen consist chiefly of proteoses and globulins. Some cases of so-called idiopathic or physiologic albuminuria in the male are merely vesicular albuminuria which is really globulinuria and is the result of the expulsion of vesicular contents in the urine at the end of urination. Thus albuminuria of adolescence in the male may also in some cases be due to hypersecretion of the prostate and seminal vesicles

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[11] Thomas, B. A. and Harrison, L. W.: J. Urol., 1: 59–74, 1917.

Studies by Brach on the contents of the seminal vesicles in cadavers showed no sperm in the seminal vesicles[12] in almost 50 per cent of a total of 500 examined There are other reports of postmortem examinations in men in which very few or no sperm were found in the seminal vesicles

The importance of the seminal vesicles as the chief source of fructose indicates they are not only a receptacle for spermatozoa but also have another function, i e production of a secretion which activates the spermatozoa It is the opinion of many that the seminal vesicles are a reservoir for the spermatozoa but that they are not the only reservoir and that the ampulla of the vas also serves the same function Thus the seminal vesicles have a dual function—that of secretion and also as a receptacle for the spermatozoa

SEMINAL VESICULITIS, PUS TUBES IN THE MALE (BELFIELD)

Seminal vesiculitis was a subject frequently discussed at urologic meetings up to 15 or 20 years ago Discussions concerning the seminal vesicles appear relatively infrequent in the literature now because pathology of these structures is apparently not considered important Although seminal vesiculitis was undoubtedly overemphasized in the past it is well to remember that these are rather large structures in close association with the bladder neck, urethra and prostate and that the infection of the seminal vesicles is usually present in association with infections of the prostate Infections of the seminal vesicles often produce symptoms of bladder neck disease

When doing retropubic prostatectomy we frequently expose the seminal vesicles They are subtrigonal and occasionally quite large We remove the upper portion of the vesicles in many cases for the purpose of getting a good functional end result

VASOTOMY

This is the term coined by Belfield for the injection of the seminal vesicles through an incision in the scrotal vas This was intended to medicate the infected seminal vesicles However, its value now is merely that of radiography of the seminal vesicles and much has been learned from this procedure Thus if one will look carefully at radiograms of the seminal vesicles it will be noted that the ampulla of the vas enters the neck of the seminal vesicles similar to the insertion of the ureter into the bladder, also that the ejaculatory duct is a continuation of the seminal vesicle and is not formed by the junction of the ampulla of the vas and seminal vesicle, as usually stated There is therefore a valid reason for Belfield's contention that the seminal vesicle, which is a tubular structure in the human, is a reservoir for the spermatozoa

These are some of the highlights on the seminal duct There is much more that has not been covered I have thoroughly enjoyed reviewing this subject and hope it is of interest to you as it has been to me

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[12] Brach, W Ztschr f urol Chir , 12 403, 1923

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TRANSVESICO-CAPSULAR PROSTATIC ADENOMECTOMY (TRANSCOMMISSURAL): PRELIMINARY REPORT ON 80 CASES

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Since Freyer's prostatectomy was published, numerous techniques have been devised for prostatic adenomectomy. All methods have their good points but, in our opinion, too much is left to nature's goodwill, mainly hemostasis, which in most procedures is not feasible because of inadequate exposure. For that reason we adopted the operation described hereafter, bearing in mind that excess bleeding during and after prostatic adenomectomy comes from the two vesicoprostatic arteries, the bladder neck, the vesical mucosa and the superior and lateral capsular veins.

To our knowledge a few techniques similar to ours have been described, but all with which we are familiar were reported under the name of retropubic prostatectomy.[1-4]

We think that "transvesico-capsular prostatic adenomectomy" is a suitable term for the procedure. It could also be called "transcommissural prostatic adenomectomy."

In this operation, the exposure is adequate; it allows a direct view on the whole region; it permits for all practical purposes complete hemostasis, leaving a slight ooze which tapers off in a matter of 24 to 36 hours; it also affords access to stone, diverticulum, interureteral ridges, tumors etc; it is not traumatizing because the pubis, the bladder and the peritoneum are well protected. The operation is not difficult and can be easily performed on any patient whether he is short or fat, or both.

INSTRUMENTATION

No special instrumentation is needed outside of a self-retaining abdominal retractor, a flexible blade retractor, a Beckman's autostatic retractor and long curved scissors. A French needle of the Reverdin type, called the "Bergeret" needle, is very handy to place the deep ligatures but these can be placed with the usual instrumentation.

TECHNIQUE

Our cases were done either under general anesthesia or under spinal anesthesia, this having no direct relation to the operation itself.

While the anesthesia is being induced, the urethra is irrigated with zephiran

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[1] Hand, J. R. and Sullivan, A. W.: Retropubic prostatectomy: An analysis of 100 cases. J. A. M. A., 145: 1313–1321, 1951.

[2] Jacobs, L. C. and Cooper, E. J.: Prevesical prostatectomy. Urol. & Cutan. Rev., 37: 729–732, 1933.

[3] Ward, R. O.: Vesicocapsular prostatectomy. Lancet, 1: 472–474, 1948.

[4] Carruthers, C. M.: Retropubic prostatectomy, modification of Millin operative technique. J. Internat. College of Surg., 15: 639–645, 1951.

chloride 1:1000 and then a soft rubber catheter is inserted into the bladder. The bladder is irrigated with normal saline solution, after which 50 cc zephiran chloride 1:1000 are introduced into the bladder and left there, the catheter being removed. Complete sterilization of the operative field is then obtained by alcohol and metaphen solution.

The vasa deferentia are ligated and divided.

A midline incision is made from the pubis to the umbilicus. The bladder and the space of Retzius are exposed. The superficial veins of the space of Retzius are ligated behind the pubis and on the bladder and are resected.

A trocar, connected to a suction pump, is then introduced in the bladder, immediately above the neck, so as to empty the latter completely. Since the solution has been in the bladder for 15 to 20 minutes, the cavity, for all practical purposes, is sterile.

A stab wound incision is made where the trocar was inserted. The index finger is introduced through this opening towards the prostatic urethra; the mucosa of the prostatic urethra is broken anteriorly on both sides, as in the well established suprapubic technique: This is done in order to avoid profuse bleeding and to enter the normal prostatocapsular cleavage bed.

Then, the prostatic capsule, the neck of the bladder and the bladder are incised on the anterior wall for approximately 3 inches (fig. 1, *A*), and the retractor in the form of a wide, flexible blade is placed in the upper part of the bladder so as to keep it opened and retracted back, thus giving a complete exposure of the region operated upon. The adenoma is then bluntly dissected with the index finger first laterally, then posteriorly, avoiding the urethra and the bladder neck (fig. 1, *B*).

Long curved scissors are used to divide the urethra near the apex of the adenoma (fig. 2, *A*).

The same scissors are used to divide the bladder mucosa which is incised all around the lateral and the median lobes, so as to have a good, clean incision (fig. 2, *B*).

If the capsular veins bleed too much, a catgut suture is placed through the

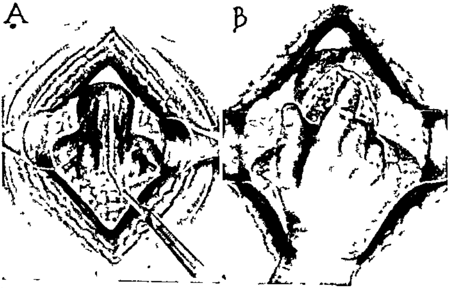

FIG. 1. *A*, incision of prostatic capsule, bladder neck and lower anterior wall of bladder. *B*, index finger liberating adenoma on sides and underneath avoiding urethra and bladder neck.

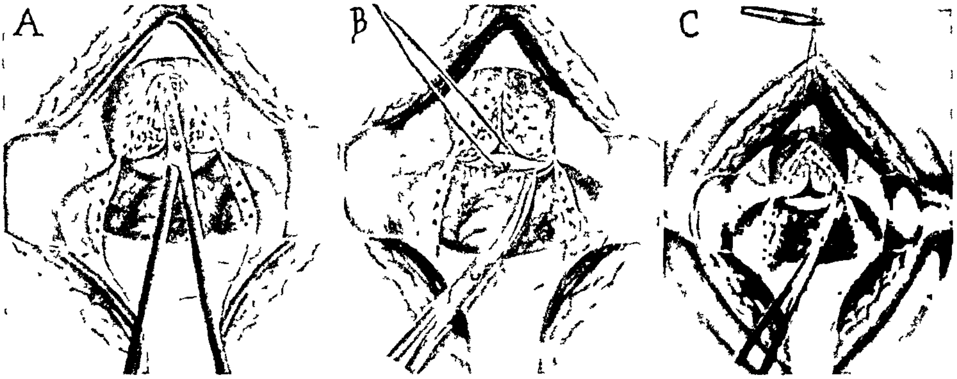

FIG. 2. *A*, long curved scissors dividing adenoma from urethra. *B*, same scissors dividing bladder mucosa from lateral and posterior prostatic lobes. *C*, catgut placed in lower angle of wound for temporary hemostasis. Same scissors divide adenoma from bladder neck.

capsule at the lower part of the incision and pulled upwards, the compression being sufficient to produce temporary hemostasis. After this is done, the adenoma is lifted up from its capsular bed and brought into the bladder and sharp dissection scissors are used to free it from the bladder neck (fig. 2, *C*). The adenoma, completely freed, is then removed. If any small adenomas are left, they can be seen and removed either with the finger or with the scissors.

The main bleeding points are now completely visualized as the exposure is wide. The two main arteries, that is the two vesicoprostatic arteries, are ligated. They can usually be seen spurting very clearly on the lateral aspects of the bladder neck, between 1 and 3 o'clock on the right and between 9 and 11 o'clock on the left. They are ligated with 0 chromic catgut with a figure of eight stitch, so as to be secure. If there are any other spurters, they are ligated. The bleeding that occurs in the vicinity of the urethra is stopped by the catheter which will be placed later.

If any pathological process is found in the bladder, especially an interureteric ridge, it is resected bluntly with the scissors. The posterior lip of the bladder neck is then resected properly and either continuous suture, interrupted mattress or figure of eight sutures are placed on the latter, thus completing the hemostasis.

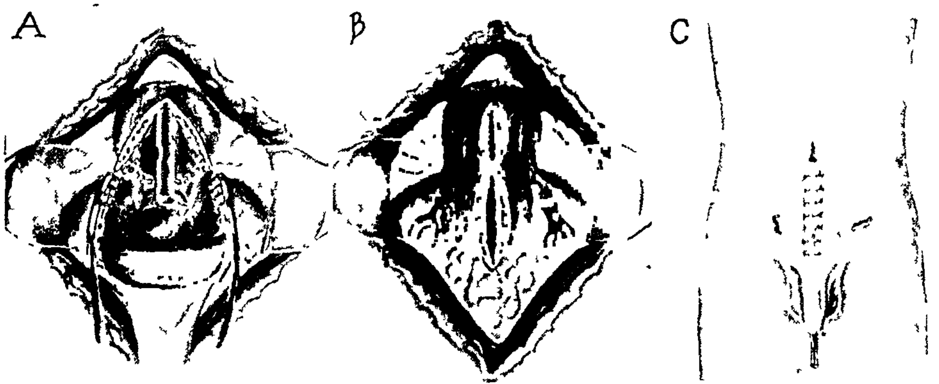

FIG. 3. *A*, visualization of bladder and of prostatic bed with ligatures placed, reconstituted bladder neck sutured and catheter in good position. *B*, sutures approximating and adjusting anterior part of bladder neck. *C*, wound closed with drains coming through lateral stab wounds, catheter held by sutures to penile foreskin.

A No. 24 multiple eye Marion catheter, the tip of which has been cut off to afford better drainage and avoid irritative bladder spasms after the operation, is introduced through the urethra with the eyed portion placed half in the bladder and half in the prostatic bed. No topical hemostatics of any kind are used (fig. 3, *A*).

When the catheter has been adjusted, it is secured in good position and held there by two silk stitches sutured to the penile foreskin, this causing absolutely no pain or discomfort.

Two stitches are now placed on the bladder neck in order to be sure that this particular portion is well approximated so that one finger can easily pass through the neck opening (fig. 3, *B*).

The prostatic capsule and the bladder are closed by two layers of continuous sutures, using No. 0 chromic catgut.

A stab wound is made on either side of the recti muscles through which Penrose drains placed in the space of Retzius are drawn out. The median incision is closed completely (fig. 3, *C*).

The wound is isolated with a dressing covered by adhesive tape. Sterile gauze is also used to cover the two drains.

The bladder is now irrigated. If by chance a few clots remain or a tendency to clotting is noted, 30 cc of a 1 per cent sodium citrate solution are introduced in the bladder to make sure that no clots form during the return of the patient from the operating room to his bed.

POSTOPERATIVE CARE

Irrigations are done, if needed; if not, as is the rule in most cases, the catheter is just left alone in a urinal and looked over every hour or so to verify its good function.

The patient is permitted out of bed either the night of the operation or the next day. The dressing covering the drains is not touched until the second postoperative day. The two drains are shortened a couple of inches every day so that on the fifth postoperative day, both drains are completely removed. The main dressing is not touched until the eighth postoperative day, when it is removed with the stitches. The catheter is removed on the fifth or sixth day.

If the patient has discomfort or pain the day of the operation and the next day, morphine or other drugs are given, but on no occasion have we used more than one to two quarter grains of morphine to make the patient comfortable. Streptomycin and penicillin are given routinely.

After 48 hours, if the Marion catheter causes pain, it is removed and replaced by a No. 22 Foley catheter because, for the ambulant patient, it is more comfortable than the rigid Marion catheter.

ANALYSIS OF CASES

An analysis of our cases is presented in tables 1 to 8.

We had 1 case of secondary hemorrhage, 6 cases of urinary leakage and wound infection, 1 case of incontinence, 3 cases of bronchopneumonia one of which was fatal and 5 cases of phlebitis (table 4). At no time did we encounter shock, either

TABLE 1. *Ages*

	Per cent
4 patients between 45 and 60 years of age	5.0
34 patients between 60 and 70 years of age	42.5
28 patients between 70 and 80 years of age	35.0
14 patients between 80 and 90 years of age	17.5

TABLE 2. *Other urinary conditions present*

	Cases	Per cent
Infection	44	55.0
Bladder tumor	1	1.2
Diverticulum	1	1.2
Calculi	5	6.3
Impaired renal function	7	8.7
Prostatic obstruction only	22	27.6

TABLE 3. *Other systemic conditions present*

	Cases	Per cent
Chronic myeloid leukemia*	1	1.2
High blood pressure and arteriosclerosis	10	12.5
Cardiac conditions (i.e. coronary, partial block, enlarged heart etc	25	31.3
Other conditions of secondary importance, (i.e. diabetes, pulmonary, varicosed veins etc.)	12	15.0
Healthy and good risks	32	40.0
Total: Good risks	32	40.0
Poor risks	48	60.0

* The one case of myeloid leukemia had 120,000 white blood cells and a bleeding time of 32 minutes. No postoperative hemorrhage, immediate or secondary, was encountered in this case.

TABLE 4. *Postoperative complications encountered*

	Cases	Per cent
Shock (primary or secondary)	0	0
Immediate postoperative hemorrhage	0	0
Secondary hemorrhage	1	1.2
Urinary leakage and wound infection	6	7.5
Urinary infection or septicemia	0	0
Fistulas	0	0
Osteitis pubis	0	0
Incontinence	1	1.2
Residual urine	0	0
Pulmonary (bronchopneumonia)	3	3.8
Circulatory (phlebitis)	5	6.3
Uneventful recovery	64	80.0

TABLE 5 *Number of days of postoperative catheter drainage*

	Days
Maximum*	30
Minimum	5
Average	7.5

* The maximum number of days in which a patient was on postoperative catheter drainage was 30 days because of the 6 patients who had urinary leakage and wound infection

TABLE 6 *Healing of the wound*

	Cases	Per cent
Primary healing	74	92.5
Secondary healing	6	7.5

TABLE 7 *Number of days of hospitalization*

	Days
Longest hospitalization*	33
Shortest hospitalization	9
Average	12.3

* The hospitalization was lengthened by those patients who had urinary leakage or other postoperative complications, i.e. phlebitis, etc

TABLE 8 *Results*

	Cases	Per cent
Good results	64	80
Complications	15	18.8
Mortality	1	1.2

FIG 4

primary or secondary, immediate postoperative hemorrhage, urinary infection, fistulas, osteitis pubis or residual urine The case of secondary hemorrhage happened on a patient 83 years old, very nervous, who was always tense and complained of bladder spasms, the hemorrhage was not serious and as soon as the blood clots were evacuated, the bleeding stopped The 6 cases of urinary leakage and wound infection occurred in the first 25 cases Catheter drainage was re instituted and the wounds healed secondarily. The case of incontinence lasted for about 3 weeks but actually the patient now has no symptoms whatsoever. Our one fatality was bronchopneumonia in a man of 89 years of age, 12 days after operation; the pulmonary complication appeared the day before he was supposed to leave the hospital. Autopsy indicated that the urinary tract was negative.

We had uneventful recoveries in 64 cases.

In the last 55 cases done, the technique was more to the point and in no case was the catheter in place longer than 6 days nor hospitalization greater than 12 days.

We had 79 cures or 98.8 per cent and 1 death or a 1.2 per cent mortality.

None of these patients actually have had any difficulty in voiding. In most of them, the urine was clear and free of pus within 3 to 4 weeks; some still have to get up once a night and urinate every 3 to 4 hours during the day. None have residual urine.

Figure 4 depicts a urethrocystogram made 2 months after operation; a good urinary stream can be observed.

Sexual potency was undisturbed when present before the operation.

CONCLUSIONS

A technique has been fully described for prostatic adenomectomy. It can be called the transvesico-capsular prostatectomy or the trans-commissural prostatic adenomectomy.

The purpose of the operation is to avoid serious bleeding during the operation by doing the adenomectomy as anatomically as possible; i.e. the dissection of the adenoma from its bed followed by the division of the urethra, the vesical mucosa and the bladder neck, all these stages being done under direct vision.

It permits practically complete hemostasis by adequate ligature of the two vesicoprostatic arteries and the suture of the bladder mucosa, thus avoiding immediate postoperative hemorrhage.

It permits complete reconstitution of the bladder neck thereby avoiding late strictures that often follow other techniques. The surgeon is afforded an opportunity to correct other pathological processes when present.

The operation is nontraumatizing as nothing is done blindly, and trauma to the pubis or the peritoneum is avoided completely.

The operation can be done satisfactorily on fat and short individuals.

The postoperative course is smooth, the immediate and late results are good, and follow-up examinations reveal no late complications.

The number of days of catheter drainage is short and so is the hospital stay.

Our cases were not chosen; they were met as they came. Half of the cases were ward cases and the other half were private, this making no particular difference.

SUMMARY

A technique for prostatic adenomectomy has been described. It can be called the transvesico-capsular prostatic adenomectomy or the transcommissural prostatic adenomectomy. A preliminary report has been made on 80 cases with immediate and late follow-up.

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THE SAFETY OF WATER IRRIGATION IN TRANSURETHRAL PROSTATECTOMY

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The choice between water and a nonhemolytic solution has divided resectionists We feel it necessary to justify ourselves since we have continued to use water in spite of its condemnation by some authorities Outstanding resectionists, having seen hemolysis and lower nephron nephrosis with water irrigation, have turned to glucose, mannitol, and other nonhemolytic solutions So we have examined our own experience, to see if we should change from the use of water

THEORETIC CONSIDERATIONS

Experimentally it is very hard to produce anuria by lysis of blood alone Some other factor must be present, such as shock, poor renal function, or direct renal damage (as by temporary venous or arterial occlusion) Also, the reported clinical experience, while showing that hemolysis has been present in the cases with anuria, does not always emphasize the cases with hemolysis of similar magnitude in which anuria does not occur A patient one of us operated upon in 1946 had a serum hemoglobin level of 690 mg /100 cc with cyanosis and later, icterus, but oliguria or anuria did not develop

The disadvantage of the nonhemolytic solution is its preservation of the red blood cell which, by refracting light, limits visibility Perhaps for the highly skilled resectionist who can distinguish the tissue layers with great ease, this limitation is not serious But the man who does a resection less often than once a week needs good visibility so that he can readily identify the correct plane The highly skilled resectionist operates upon large glands in which the true prostate is greatly thinned, so that entrance of water into the periprostatic venous sinuses will occur more often Most resectionists, on the other hand, limit themselves to glands weighing 40 or 50 gm and so maintain a thicker bulwark of true prostate between the margin of resected adenoma and the capsular veins

CLINICAL EXPERIENCE

On the University of California service (University and Franklin Hospitals) in the 7 years from May 1947 to April 1953 inclusive, 509 resections were done by the resident and visiting staffs There were 8 deaths (1 6 per cent) Eight patients had postoperative anuria oliguria, usually with other complications Three of the eight died The other 5 deaths, uncomplicated by renal shutdown, were caused by pulmonary embolus, cerebral thrombosis, ureteral obstruction, cardiac failure, and coronary occlusion

CASES OF OLIGURIA ANURIA

Case 1 M F, 75 years old, had excessive bleeding during and after transurethral resection, with a possibility of extraperitoneal extravasation Three units of blood and two units of plasma did not bring his blood pressure above 100 mm. Hg. systolic. He was anuric on the second postoperative day and died 6 days later in oliguria.

Case 2. O. S., a 70-year-old patient, had an easy 24 gm. resection with slightly more than 100 cc blood loss. However on the next day during treatment for atelectasis, he aspirated vomitus. Hypotension followed, then oliguria, but his phenolsulfonphthalein excretion was 35 per cent in one hour on the fourth day. He died on the twenty-fourth day, with multiple arterial emboli.

Case 3. F. K., 67 years old, had excessive bleeding after resection. In spite of cystostomy and packing, bleeding caused shock with subsequent oliguria. The sigmoid was perforated. Anuria, unresponsive to fluid control and cross-transfusion, ended in death on the eighteenth postoperative day.

Case 4. E. S., a 71-year-old man, had a 33 gm. resection with 241 cc blood loss. There was cyanosis, tachycardia, and transient hypertension followed by marked hypotension, and oliguria lasting 3 days with 490 cc the lowest daily output. He was discharged convalescent on the fourteenth day.

Case 5. S. K., 75 years old, had perforation of the capsule after 30 gm. had been resected. The blood pressure rose to 160 so that the operation was stopped. He then appeared shocky and cyanotic. At that time, however, serum hemoglobin was only 60 mg./100 cc. He was returned for fulguration, then sent to the operating room for cystostomy and packing of the fossa. This was accompanied by hypotension. Oliguria followed, lasting 8 to 10 days. He was discharged on the twenty-seventh day.

Case 6. C. V., a 65-year-old man, had a small resection with considerable bleeding and a recognized capsular perforation. Suprapubic packing was done. Oliguria, followed by anuria, lasted to the sixteenth postoperative day. He had thrombophlebitis and pulmonary infarcts, but was discharged on the forty-ninth day.

Case 7. W. H., 55 years old, had his first resection ended after 30 minutes because of clinical signs of shock without hypotension. Six days later, 50 gm. were resected. Chills were observed after 250 cc of whole blood was given, so the transfusion was stopped. There was further bleeding and hypotension after operation. Oliguria lasted 13 days. The patient was discharged on the twenty-third day.

Case 8. H. D., 68 years old, had extravasation under the trigone and uncontrollable bleeding during transurethral resection. Cystostomy and packing controlled the bleeding. Oliguria (about 500 cc daily output) was followed by diuresis on the eleventh day. He was discharged on the twenty-fifth postoperative day.

These patients all had severe hypotension, often with frank shock, extravasation, and such bleeding that open packing was required. The first patient who died had severe hemorrhagic shock with prolonged hypotension. The second death followed hypotension from aspiration of vomitus a day after an operation in which there was little opportunity for hemolysis. The other patient who expired had severe hemorrhagic shock, requiring suprapubic packing during which the sigmoid was perforated. In none of these did hemolysis appear to be an important factor in causing death.

The serum hemoglobin level unfortunately was determined in only one patient (case 5), but in this man it was not very high (60 mg./100 cc) and does not account for the oliguria, which probably was due to hypotension during the open packing of the fossa.

Case 4 fits best into the classical syndrome of the hemolytic reaction (cyanosis, tachycardia, transient hypertension followed by hypotension), but this man also had a rather heavy loss of blood, and his oliguria was mild and lasted only 3 days.

Study of these 8 cases suggests that hemolysis does not necessarily play a major precipitating part in post-resection oliguria.

SUMMARY AND CONCLUSIONS

Study of 8 cases of renal shutdown(5 temporary and 3 permanent) in 509 resections of the prostate on the University of California services suggests that hemolysis by water as an irrigating fluid is not a critical factor in anuria or oliguria. Severe blood loss with hypotension and shock are more frequently implicated.

Resection of large glands with thinned surgical capsules more often involves opening into venous sinuses. This explains the preference for a nonhemolytic solution by skilled resectionists, but does not mean that it is needed for the smaller adenoma enclosed in a thicker prostate.

Nonhemolytic irrigating solutions tend to obscure vision, making identification of exact tissue planes more difficult, especially for the occasional resectionist.

The use of water as the routine irrigating solution for transurethral resections will be continued because the advantages of good visibility seem to outweigh the dangers of hemolysis.

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POSSIBLE SIGNIFICANCE OF THE PROSTATIC SECRETION ACID PHOSPHATASE AS A DIAGNOSTIC AND A PROGNOSTIC INDEX IN CARCINOMA OF THE PROSTATE

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The most reliable method in diagnosing carcinoma of the prostate is digital palpation of the prostate gland rectally. It has been estimated that an expert can detect in this clinical method 80 per cent of moderately advanced cases of prostatic carcinoma. Therefore, there has been and still is a need for a method of determining early prostatic carcinoma, and also confirming questionable findings noted on rectal palpation. Needle biopsy, transurethral resection, perineal biopsy, and study of Papanicolaou's preparation of cells in the prostatic fluid have not been entirely adequate, or have necessitated an involved procedure to confirm the diagnosis.

It is known that serum acid phosphatase level is not elevated in carcinoma of the prostate as long as the tumor is confined within the prostatic capsule. Even after extension or metastasis of the prostatic carcinoma, the serum acid phosphatase level is elevated in only 80 per cent of cases. Therefore, this determination is not satisfactory in the diagnosis of early prostatic carcinoma.

It is the object of this study to present for consideration a new simple test which may be useful in confirming, and possibly in detecting the presence of suspected or unsuspected carcinoma. For this purpose, we utilize the difference in the level of prostatic secretion acid phosphatase before and following stilbesterol administration. A review of previous works on this subject suggesting the possibility of this test is as follows:

Huggins[1] was the first one who studied the histological changes in the malignant prostate following the anti-androgen treatment for carcinoma of the prostate, and found a diminution in the size of the acini with areas of nuclear destruction. These findings were confirmed later and studied thoroughly by Schenken, Burns and Kahle,[2] Heckel and Kretschmer,[3] Gilbert and Margolis,[4] Graves and Cross,[5] Moore and Wattenberg,[6] Fergusson and Frank.[7] These changes start rapidly within the first week of stilbesterol administration and are characterized by the

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[1] Huggins, Charles: Effect of orchiectomy and irradiation on cancer of the prostate. Ann. Surg., **115:** 1192, 1942.

[2] Schenken, J. R., Burns, E. L. and Kahle, P. J.: The effect of diethylstilbesterol dipropionate on carcinoma of the prostate gland. J. Urol., **48:** 99, 1942.

[3] Heckel, N. J. and Kretschmer, H. L.: Carcinoma of the prostate treated with diethylstilbesterol. J. A. M. A., **119:** 1087, 1942.

[4] Gilbert, G. G. and Margolis, G.: Postmortem findings in carcinoma of the prostate following castration and diethylstilbesterol therapy. J. Urol., **50:** 82, 1943.

[5] Graves, R. C. and Cross, J.: Regression of lymph node metastases after orchiectomy and stilbesterol in carcinoma of the prostate. J. Urol., **51:** 59, 1944.

[6] Moore, G. F. and Wattenberg, C. A.: Breast changes due to diethylstilbesterol during treatment of cancer of prostate gland. J. A. M. A., **127:** 60, 1945.

[7] Fergusson, J. D. and Frank, L. M.: The response of prostatic carcinoma to estrogen treatment. Brit. J. Surg., **40:** 422, 1953.

appearance of small intracytoplasmic vacuoles, which push the nucleus to one side The nuclei then become condensed, hyperchromic, and pyknotic, and these degenerated swollen cells fill the alveolar spaces Ultimately, cellular destruction is followed by fibrosis, which, after a few months of treatment, predominates the picture, only here and there areas of malignant cells can be seen (fig 1)

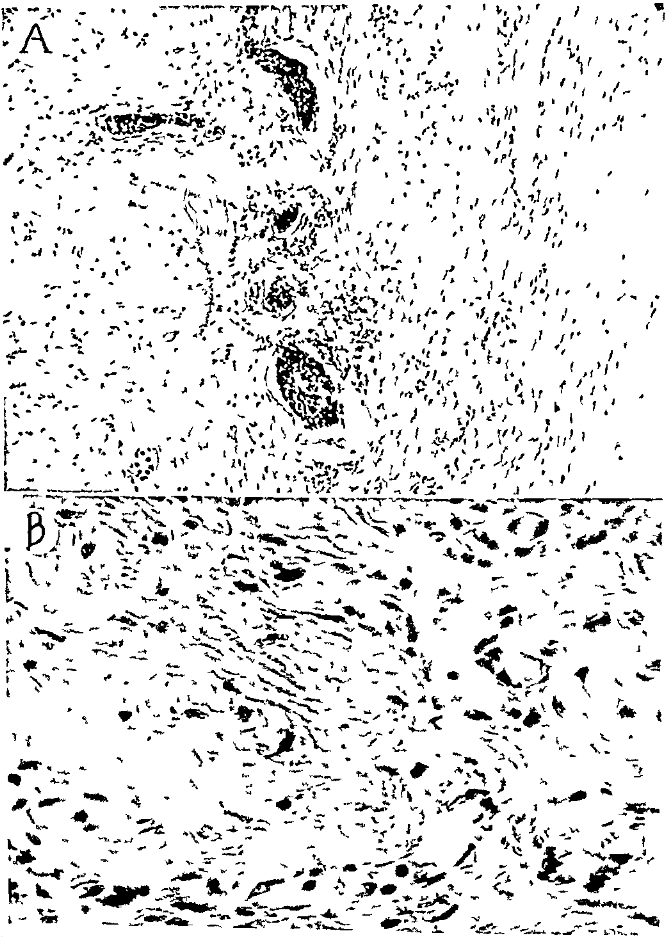

Fig 1 *A* regression in prostatic carcinoma after stilbesterol administration × 80 *B*, regression in prostatic carcinoma after stilbesterol administration × 400

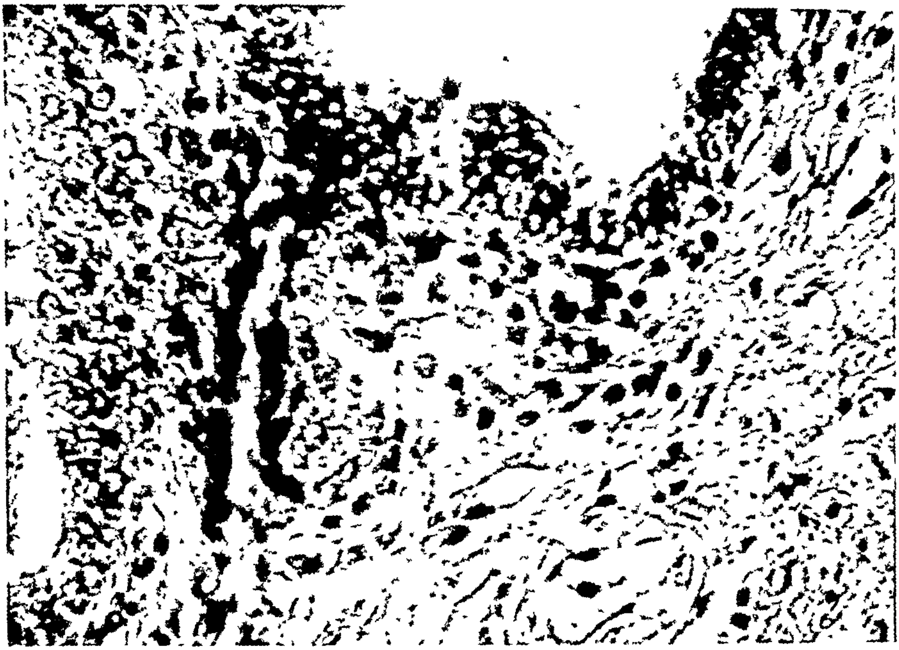

FIG. 2. Metaplasia in benign prostatic hypertrophy following stilbesterol administration. × 400.

On the other hand, Moore and McLellan[8] found that estrogen administration for 10 days in benign prostatic hypertrophy causes metaplasia of the prostatic urethra and ductal epithelium, but little changes in the glandular epithelium (fig. 2).

Huggins,[9] while studying the etiology of benign hypertrophy of the prostate, discussed the problem thoroughly and found that estrogen administration in benign hypertrophy of the prostate, in dosage sufficient to cause breast growth in man, causes no decrease in the amount of enzymic concentration of the prostatic fluid. Also, it has been shown by Gutman and Gutman[10, 11] that the acid phosphatase in the prostate gland is negligable before puberty, and only reaches its normal level at puberty. They found also that the level of the prostate gland acid phosphatase can be elevated by the injection of testosterone and decreased after bilateral orchiectomy. They concluded that prostatic acid phosphatase can be taken as an index to the activity of the prostate gland.

With these facts in mind, and since it has been shown histologically that there is a difference in response of the prostate gland to stilbesterol, we reasoned that there might be a definite parallel change in the level of the prostatic secretion acid phosphatase following stilbesterol administration. The destruction seen in

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[8] Moore, R. A. and McLellan, A. M.: A histological study of the effect of the sex hormones on the human prostate. J. Urol., **40**: 460, 1938.

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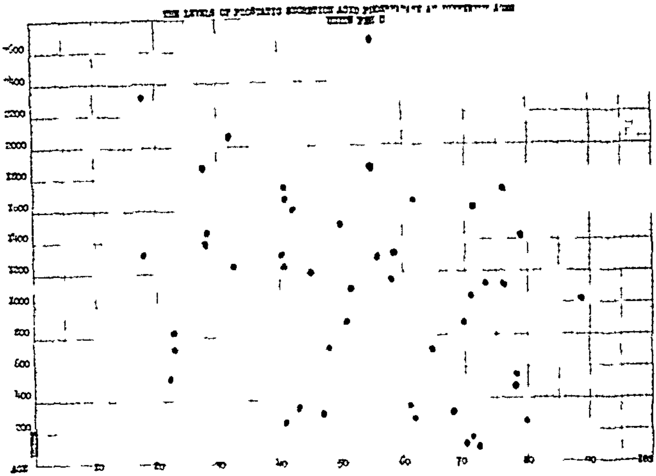

FIG 3

carcinoma of the prostate following stilbesterol administration, which is not found in benign glands, might be accompanied or preceded by a remarkable reduction in the prostatic secretion acid phosphatase, which is the index to the activity of the prostate gland

MATERIALS AND METHOD

This preliminary report, comprised of 23 cases, includes 1) four patients with normal prostate, 2) five patients clinically diagnosed as having chronic prostatitis, 3) five patients who clinically were diagnosed as having benign prostatic hypertrophy, two of them confirmed pathologically after open prostatectomy, and 4) nine patients who clinically were diagnosed as having advanced carcinoma of the prostate, three of them with demonstrable osteoblastic metastases

The acid phosphatase level in the prostatic fluid was determined on each case by collecting prostatic fluid following rectal massage of the prostate Twenty cubic mm of the prostatic fluid were measured using a hemoglobinometer pipette, and diluted with 2 cc of distilled water The method used to determine acid phosphatase activity in the prostatic secretion was Shinowara method,[12] which is a simple micro photo electric method, used to determine phosphatase activity in the body fluids without necessitating modifications required by other methods The results were reported as Shinowara units per cubic centimeter of the prostatic fluid It is worthwhile to mention that with this method, the normal level of serum acid phosphatase ranges from 0 0 to 1 1 units per 100 cc of the serum,

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[12] Shinowara, G Y and Jones L M The estimation of serum inorganic phosphatase and acid and alkaline phosphatase activity Biol Chem , 142 921 1942

TABLE 1. *The effect of stilbesterol administration on the level of prostatic fluid acid phosphatase*

No.	Name	Age	Diagnosis	Method of Diagnosis	Serum Acid Phosphatase U./100 cc.	Prostatic Fluid Acid Phosphatase U./cc. before Treatment	Prostatic Fluid Acid Phosphatase U./cc. after Treatment
1	D.A.	31	Normal	Clinical		1378	2159
2	B.J.	53	"	"		1800	860
3	J.S.	28	"	"		1770	1040
4	L.H.	32	"	"		2458	1085
5	W.S.	58	Chronic prostatitis	"	0.0	1040	1080
6	L.W.	24	"	"		345	710
7	L.M.	28	"	"		1354	1088
8	C.B.	47	"	"	0.9	46	265
9	C.H.	45	"	"		1169	90
10	J.V.	70	B.P.H.	"	0.8	783	1500
11	A.W.	55	"	"	0.0	1755	1974
12	K.N.	58	"	"	0.6	1305	1980
13	C.M.	70	"	Pathological	1.2	63	186
14	C.F.	58	"	"	0.3	1038	1280
15	T.R.	82	Carcinoma	Clinical	0.7	1122	124
16	H.S.	63	"	"	1.0	1480	186
17	A.B.	88	"	"	1.9	990	340
18	H.R.	83	"	"	1.0	215	15
19	W.R.	64	"	Metastases	0.9	78	5
20	J.A.	67	"	"	0.6	1118	930
21	P.G.	76	"	"	4.1	1730	64
22	A.S.	70	"	Clinical	0.7	268	21
23	C.F.	63	"	"	0.4	1560	306

while the level of prostatic secretion acid phosphatase in normal individuals from 17 to 90 years old (70 cases) were 500–2600 units per cubic centimeters of the prostatic fluid.

Recently, Schwartz, Asimov, and Wortiz[13] discovered definite biochemical differences in between the acid phosphatase from apool of a malignant prostate, and that from a normal gland. The most striking differences were in the pH. optimum, the patern of hydrolysis of equimolecular concentration of several substrate, and the dissociation constant of the assumed intermediate enzyme complex.

In all of the 23 patients the level of the prostatic secretion acid phosphatase was determined and then stilbesterol was administered in 10 mg. daily doses for a week, after which the acid phosphatase level in the prostatic fluid was determined again.

FINDINGS AND DISCUSSION

There was no remarkable correlation between the level of the prostatic secretion acid phosphatase and the age of individual with normal prostate (fig. 3).

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[13] Schwartz, M. K., Asimov, I. and Wortiz, H. H.: The action of acid phosphatase from cancerous and non-cancerous human prostate on various substrates. Cancer, 6: 924, 1953.

There was no significant difference in pretreatment level of the prostatic secretion acid phosphatase in either benign prostatic hypertrophy or carcinoma of the prostate. There were almost always low levels in chronic prostatitis.

After administration of stilbesterol for 7 days, the patients with carcinoma of the prostate showed a striking reduction in the level of the prostatic fluid acid phosphatase (table 1).

After stilbesterol administration, patients with normal prostates or with nonmalignant diseases of the prostate showed no significant reduction in the level of prostatic secretion acid phosphatase. In some cases of benign hypertrophy of the prostate there was slight elevation (table 1).

There was no demonstrable correlation between the level of serum acid phosphatase and prostatic fluid acid phosphatase.

The reduction in the level of prostatic secretion acid phosphatase was more striking in cases of carcinoma of the prostate which showed a dramatic response to anti-androgen treatment (case 21), just the opposite of the resistant cases (cases 17 and 20).

SUMMARY

A simple laboratory method to diagnose carcinoma of the prostate was described.

The marked reduction in the level of prostatic secretion acid phosphatase following stilbesterol administration in carcinoma of the prostate may be of value in diagnosing carcinoma of the prostate, since no such striking reduction in this level could be demonstrated in nonmalignant glands.

This simple test may be useful also to determine the androgenic activity of various synthetic estrogens, and to detect the resistant cases of carcinoma of the prostate to anti-androgen treatment, so other more effective treatment can be instituted.

I wish to extend my very sincere thanks to Dr. W. N. Taylor, to Dr. J. N. Taylor, Ohio State University, and to G. Shinowara, Ph. D., for their valuable help and suggestions.

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ADVANCED CARCINOMA OF THE PROSTATE: AN UNUSUAL CASE STUDY

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Since 1940 the endocrine control of carcinoma of the prostate has been an acceptable method. The use of estrogens and/or orchiectomy was the first method developed and its continued use is advocated. In 1945 Huggins first published the use of adrenalectomy for removing the extragonadal source of androgens. The continued use of such a procedure, however, did not come into being until the discovery of cortisone, which can be used as replacement therapy for the adrenal gland. It is hoped that this method may become a more positive link in the control of this disease because, despite the added stimulus that has developed in the study of carcinoma of the prostate, still 90–95 per cent of all carcinoma of the prostate is too far advanced for surgical extirpation.

At the time that the first reports of successful adrenalectomies appeared in the literature, the case that we are about to present returned to our clinic with re-activation of advanced carcinoma of the prostate. He was subsequently prepared for adrenalectomy. A review of his case history seems indicated.

CASE REPORT

A 53-year-old man was first admitted to the West Roxbury V. A. Hospital on May 24, 1949, with a diagnosis of advanced carcinoma of the prostate. A bilateral orchiectomy was done on June 14, 1949, and the patient was placed on stilbesterol. The patient made slow progress and in September 1949 was re-evaluated. The condition of his disease was unchanged. On September 26, 1949 a total prostatectomy, complete cystectomy with iliac lymph gland dissection, and bilateral ureterosigmoidostomy (Coffey I) was performed by the combined perineal-abdominal approach. Pathological report was adenocarcinoma of the prostate with extension into the bladder, seminal vesicles, and right common iliac node. The patient did well postoperatively. Check-up excretory urography revealed slight bilateral hydronephrosis and hydro-ureter. The patient progressed well and was carefully followed in the out-patient clinic. He was maintained on stilbesterol.

November 1, 1951, the patient complained of edema and pain in the right thigh. Examination revealed bilateral hard inguinal lymph glands and a large mass (4 cm.) in the mid-portion of his lower abdominal incision. He was again admitted to this same hospital on November 26, 1951. Biopsy of the aforementioned areas revealed metastatic adenocarcinoma of the prostate. On December 11, 1951 bilateral adrenalectomy was done using the Peet approach. Both

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements made and the conclusions drawn by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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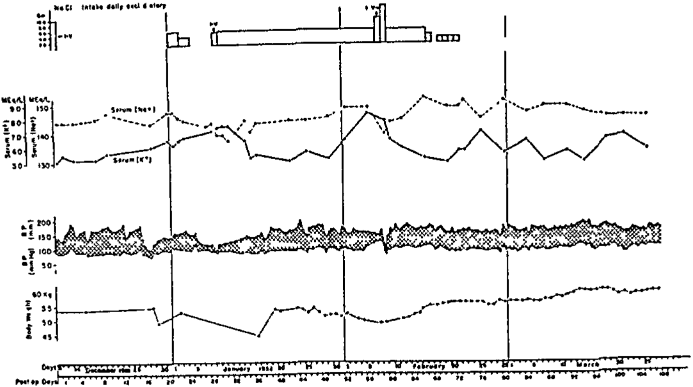

FIG. 1. Postoperative course. Shows salt intake, serum sodium, serum potassium, blood pressure and body weight levels.

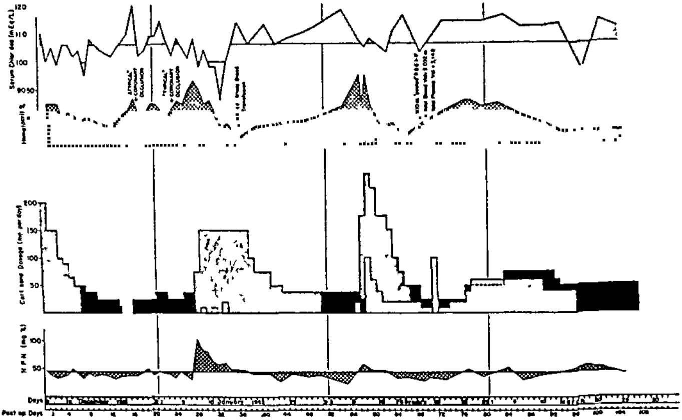

FIG. 2. Postoperative course. Serum chloride, hematocrit, cortisone dosage (darker shaded areas represent oral intake) and nonprotein nitrogen levels.

adrenal glands were grossly and microscopically normal. The postoperative course is best followed in figures 1, 2 and 3.

The postoperative course for 2 weeks was uneventful. The dosage of cortisone had been progressively reduced from its initial level of 200 mg. to a daily oral dosage level of 25 mg. At about this time for a period of 48 hours, the dosage of cortisone was omitted for purposes of epinephrine and ACTH tests, both of which were interpreted as revealing absence of functioning adrenal tissue. Within 48 hours of returning to the maintenance dose of cortisone, the patient

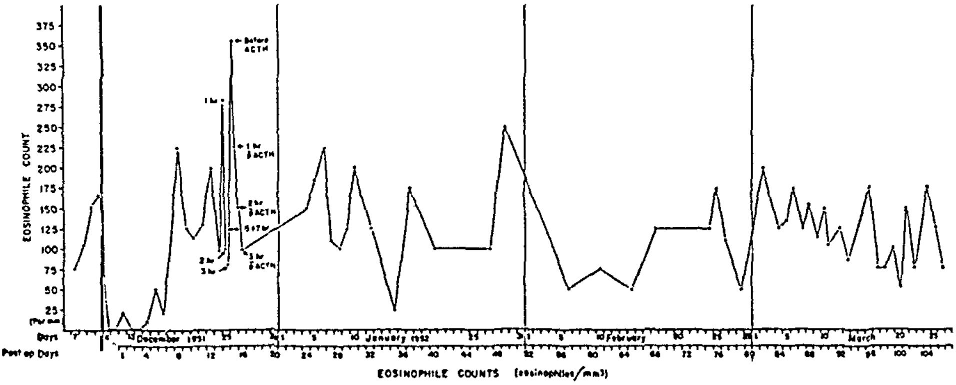

FIG. 3. Postoperative course. Eosinophile counts

commenced the first of three Addisonian crises. The first crisis was mild terminating in a second crisis, which was more severe; the third, the most severe crisis, developed after a return to normal in trying to develop a maintenance dose. Vigorous therapy was necessary to bring the patient out of these crises. They were characterized by hypotension, weakness, and laboratory studies denoting hemo concentration. The course of these three crises can be followed in figures 1 and 2. The decrease in body weight was a significant factor. By the time that the patient returned to his normal status, it was evident that the so called low cortisone maintenance doses could not be adhered to if homeostasis was to exist. The support of DOCA seemed necessary to obtain this goal. The maintenance cortisone dose finally reached was 50 mg. daily and two DOCA pellets of 75 mg. were implanted in the left infrascapular region.

DISCUSSION

Daily laboratory studies were, indeed, vital to the control of this case. Their fluctuations as seen in figures 1 and 2 could depict the oncoming crisis. As far as the acid phosphatase level was concerned, it was first noted to be elevated in November 1951 (8 KA units). Throughout the course of this patient's disease, after that time, it fluctuated markedly, however, with no known regularity, the highest level being 54 KA units. This fluctuation might be explained by the smouldering neoplastic disease, which, undoubtedly, was part of the etiology of the Addisonian crises. Another important feature in the management of this patient's Addison's disease is related to his well-functioning bilateral ureterosigmoidostomies. For it has been continually apparent, that while their function was adequate for excretion of water and most body metabolites, there was fairly constant and marked re-absorption of both sodium and chloride through the wall of the lower bowel, mainly evidenced by a rather sustained hyperchloremic type of acidosis and also allowing for maintenance of serum sodium values roughly within normal limits even in the face of an advancing severe Addisonian crisis. Daily eosinophile counts were done and as a rule were proved unsatisfactory as a means of regulating cortisone dosage. In periods of optimum patient regulation, this count remained roughly within the range of 50–175 per cubic mm. (fig. 3).

As the patient's disease progressed, it became obvious that a cure was not

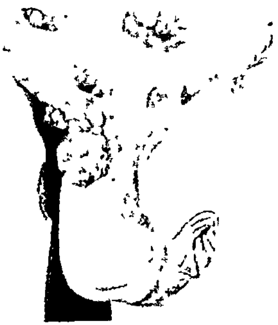

FIG. 4. Metastatic carcinoma lesions of prostate to skin

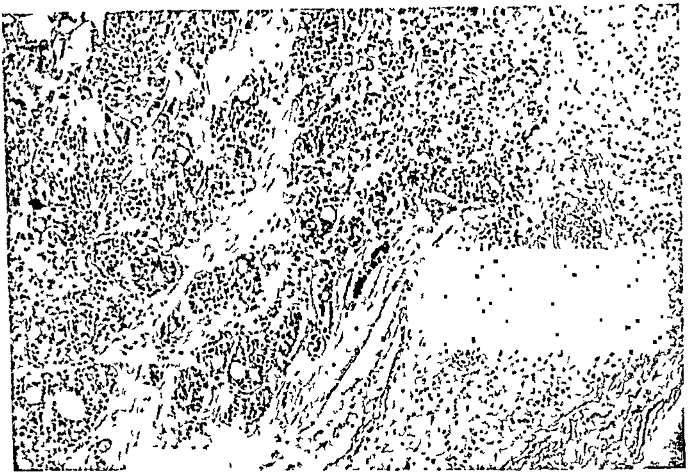

FIG 5 Low power section taken through one of biopsied skin lesions seen in figure 4 showing adenocarcinoma of prostate

obtained. Approximately two months post adrenalectomy, an unusual type of metastasis developed. This was a cutaneous metastasis on his suprapubic region and right groin area, probably as a detour, since the right common iliac nodes had been dissected. A positive biopsy of these cutaneous areas was obtained on several occasions. They can be seen grossly and microscopically in figures 4 and 5. At approximately the same time, an osteoblastic density was first noted in L2. The cutaneous metastases became so extensive that a course of roentgen therapy was initiated with some slight degree of success. This form of metastasis made it easy to follow the progression of this disease.

The remainder of this patient's life was one of intermittent hospitalizations. Several interludes were enjoyed relatively asymptomatic. The patient entered the hospital for the last time on September 4, 1952. From this time on, he began a gradual downhill course. Increasing metastases were obvious. Chronic care was begun, and the patient remained fairly comfortable until he died March 15, 1953. The patient had lived 15 months, 4 days since his bilateral adrenalectomy and just 2 months short of 4 years since the beginning of our treatment for known advanced carcinoma of the prostate.

On autopsy, all adrenal tissue was found to have been surgically removed. Metastatic adenocarcinoma of the prostate was found in the lungs, lymph nodes, liver, retroperitoneal tissues, kidney, large intestine, vertebrae, and skin.

CONCLUSIONS

There are many types of treatment for advanced carcinoma of the prostate. Using a combination of these methods, including bilateral adrenalectomy, we were able to maintain life for approximately 4 years. In this case the tumor was androgen independent for which some other method of treatment is necessary for the cure of this type of disease. This still remains unknown. Whether or not the various forms of treatment helped in palliation is debatable. An extremely interesting clinical exercise was carried out on a highly co-operative patient.

Realizing that this is only one case of advanced carcinoma of the prostate treated by bilateral adrenalectomy, its general course is similar to that of other reports in the literature. It is our opinion that cortisone alone could have given a like result.

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CLINICAL RESULTS OF THE TREATMENT OF PROSTATIC CARCINOMA OVER A TEN-YEAR PERIOD

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Treatment of carcinoma of the prostate with estrogens, orchiectomy, or both was placed on a sound basis in 1941 by the work of Huggins[1] and associates. His work proved the relationship and therapeutic significance of the sex hormones on prostatic cancer. Many subsequent studies have shown beyond doubt that androgen control therapy in the form of estrogens, orchiectomy, or both has a markedly delaying effect on carcinoma of the prostate. Most patients so treated have a remission in their pain and urinary symptoms. In some cases, the prostate is felt to be softer and smaller. Occasionally, bony metastases can be seen to improve radiographically.

Usually these effects are temporary, lasting from a few months to a few years, but they bring a welcome relief from the incapacitating symptoms of a fatal disease. The patients may have a reprieve of several comfortable and useful years of life.

It is the purpose of this paper to give the course and outcome of 122 cases of carcinoma of the prostate studied over a 10-year period. Each case in this series is a histologically proven carcinoma of the prostate. Eighty-five of the 122 have received some form of androgen control therapy. The remaining 37 had no form of specific therapy because they were treated several years before 1941.

In those cases where the malignancy is confined to the prostatic gland, radical perineal prostatectomy should be carried out. Cases in which this treatment was performed are not included in this series. Only those not suitable for radical surgery are included. All the cases reported had positive biopsies obtained either by perineal punch method or transurethral resection. Other cases treated similarly during the same period, but not proven histologically, were not included.

DISCUSSION

Of the 122 cases studied, there were 121 whites and one Negro. The youngest patient was 46 years of age, the oldest, 85. The average age incidence was 67.56 years.

There were 23 different types of signs and symptoms in the 122 cases studied. The average time from onset of symptoms to obtaining a positive biopsy was 6.7 months. The most common symptoms were frequency, nocturia, skeletal pain, and disturbance of the urinary stream. Hematuria occurred in only 12 per cent of the cases.

Read at annual meeting, Northeastern Section of the American Urological Association, Shawnee on Delaware, Pa., September 15–18, 1953.

[1] Huggins, C. and Hodges, C. V.: Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injections on serum phosphatases in metastatic carcinoma of the prostate. Cancer Research, 1: 293, 1941.

TABLE 1

	Androgen Control Group	Untreated Group
I. Bones		
a. Pelvic girdle	35	16
b. Lumbar spine	8	8
c. Ribs	8	2
d. Other bones	9	2
II. Lungs	7	3
III. Lymph nodes		
a. Inguinal	4	3
b. Supraclavicular	3	3
c. Cervical	2	1
IV. Liver	1	1
V. Bladder	0	3
VI. Penis	1	0

In those cases receiving the androgen control therapy, 41 or 48.2 per cent had demonstrable metastases when the diagnosis was made and before the therapy was begun. Twenty-one or 56 per cent of the untreated series showed metastatic disease when the primary disease was diagnosed. Table 1 shows the distribution of the metastases.

In the series of 122 cases, slides were available in 112. The vast majority of the cases reviewed were small biopsies obtained by means of a perineal punch instrument. There were a few from transurethral resections. The slides were allocated into three groups. The largest number were the adenocarcinomas with the tumor growing as small acini lined by short columnar or medium sized cuboidal cells (fig. 1, *A*). The tumor was found growing either in compact masses or as small acini invading the stroma. The second largest group was the scirrhus carcinoma (fig. 1, *B*) consisting of dark staining irregular cells growing in small masses or infiltrating cords in a dense fibrous stroma. The third group (fig. 1, *C*) consisted of an admixture of adenocarcinoma and scirrhus carcinoma. There were no transitional cell or squamous cell carcinomas. Following the above criteria, the cases were grouped as adenocarcinoma, 63 cases; scirrhus carcinoma, 34 cases; and an admixture of adenocarcinoma and scirrhus, 15 cases.

The authors have attempted to correlate the average survival of the two groups with the pathology of the tumor. Table 2 lists the androgen control group and also the untreated series.

A study was made of the serum acid and alkaline phosphatase levels in each case. These tests were usually done at the first visit of the patient, and then at most follow-up visits. Our laboratory reports these tests in King and Armstrong units. The highest level of normal is 4.0 for the acid phosphatase and 10.0 for the alkaline.

When first seen, 41 out of the 122 cases had normal acid and alkaline phosphatase levels. Elevated acid phosphatase levels were found in 47 cases, or 38.52 per cent. Normal acid phosphatase levels were found in 63 cases, or

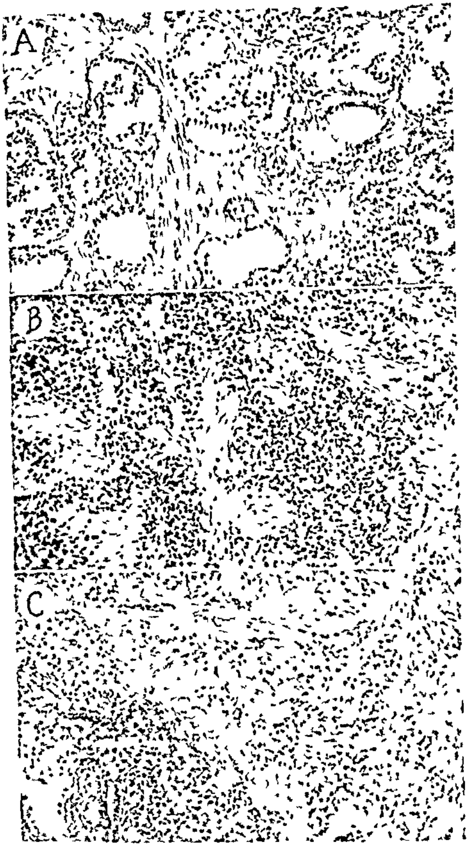

Fig 1 *A*, adenocarcinoma with typical gland formation *B*, anaplastic carcinoma infiltrating prostatic stroma *C*, admixture of adenocarcinoma and scirrhus carcinoma

Table 2 *Average months survivals*

			No of Cases
Androgen control group	Adenocarcinoma	76 28 months	45
	Scirrhus	60 96 months	27
	Mixed	44 57 months	7
Untreated group	Adenocarcinoma	31 27 months	18
	Scirrhus	23 50 months	7
	Mixed	26 87 months	8

51.63 per cent. Acid phosphatase levels were never recorded in 12 cases or 9.84 per cent.

Alkaline phosphatase was elevated in 55 cases. It was normal in 53 cases. The test was not reported in 14 cases. Acid phosphatase was thus above normal in 42.7 per cent of the cases in which a determination was obtained. Alkaline phosphatase was elevated in 50.9 per cent.

CHANGE OF ACID PHOSPHATASE

Acid phosphatase readings were followed serially in 71 of the 85 cases of carcinoma of the prostate treated by androgen control. Twenty-one of these cases were treated by stilbestrol alone, 11 by orchiectomy alone, and 39 by stilbestrol and orchiectomy combined. Fifteen of the 37 untreated cases had serial acid phosphatase readings recorded.

Of the 21 cases treated by stilbestrol alone, ten had normal acid phosphatase levels which remained normal during therapy. Six cases which had normal readings at first experienced elevated acid phosphatase levels during therapy. Only three of the 21 cases started with elevated levels and dropped to normal under therapy. One case with an elevated reading was reduced significantly, but not to normal. One case with an elevated acid phosphatase stayed elevated during the therapy.

Of the 11 cases treated by orchiectomy alone, one had a normal acid phosphatase level when first seen, and remained normal. Three were normal at first and later became elevated while under treatment. Four started with elevated levels, but came down to normal during therapy. Two with elevated levels were reduced markedly but not to normal. One case, elevated at first, remained elevated.

Of the 39 cases treated by orchiectomy and stilbestrol, 10 cases had normal acid phosphatase levels when first seen and continued to have normal levels. Twelve cases, normal at first, later became elevated while under therapy.

Nine of the 39 cases with elevated levels at first, came down to normal acid phosphatase levels under treatment. Seven cases, elevated at first, were reduced,

TABLE 3. *Changes of acid phosphatase*

Acid Phosphatase	Stilbestrol Rx.		Orchiectomy Rx.		Combined Rx.		All Androgen Control Rx.		Untreated Group	
	#	%	#	%	#	%	#	%	#	%
Remained normal	10	47.6	1	9.1	10	25.6	21	29.6	4	26.6
Change from elevated to normal	3	14.2	4	36.3	9	23.0	16	22.5	1	6.6
Down but not to normal	1	4.7	2	18.1	7	17.9	10	14.1	0	0
Total with significant reduction	4	19.0	6	54.5	16	41.0	26	36.6	1	6.6
Remained elevated	1	4.8	1	9.1	1	2.6	3	4.2	5	33.4
Change from normal to elevated ..	6	28.6	3	27.3	12	30.8	21	29.6	5	33.4
Total cases....... .	21	100%	11	100%	39	100%	71	100%	15	100%

but not to normal levels. One case with an elevated acid phosphatase stayed elevated.

Of the fifteen untreated cases with recorded serial acid phosphatase levels, four remained normal throughout the clinical course. Five cases began with normal levels but became elevated later. One case with elevated acid phosphatase at the start went to a normal phosphatase level under observation. Five cases, elevated at first, remained at elevated acid phosphatase levels throughout their course.

Summary of the significant findings then is as follows: Of 71 cases treated by one or more methods of androgen control, 16 were reduced from an elevated acid phosphatase level to a normal acid phosphatase level. This is 22.5 per cent. In addition, 10 more cases or 15 per cent had significant reductions of acid phosphatase levels, but not to normal. This is a total of 36.5 per cent which showed the effects of androgen control therapy by reduction of acid phosphatase levels. Of the fifteen untreated cases, only one case or 6.6 per cent showed this reduction.

In breaking down the androgen control treated cases into the three groups, the following results were seen: Seven out of 21 cases treated by stilbestrol alone had reduction of acid phosphatase under treatment. This is 33.3 per cent. Six out of eleven cases treated by orchiectomy alone had reduction of acid phosphatase under treatment. This is 54.5 per cent. Sixteen out of 39 cases treated by stilbestrol and orchiectomy had reductions of acid phosphatase under treatment. This is 41 per cent.

From these figures it can be seen that, judged by changes in acid phosphatase, orchiectomy with or without stilbestrol is superior therapy to stilbestrol alone. The changes in acid phosphatase are listed in table 3.

No significant conclusions can be drawn from the changes in serial alkaline phosphatase readings.

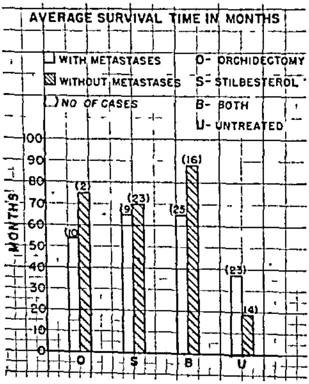

FIG. 2

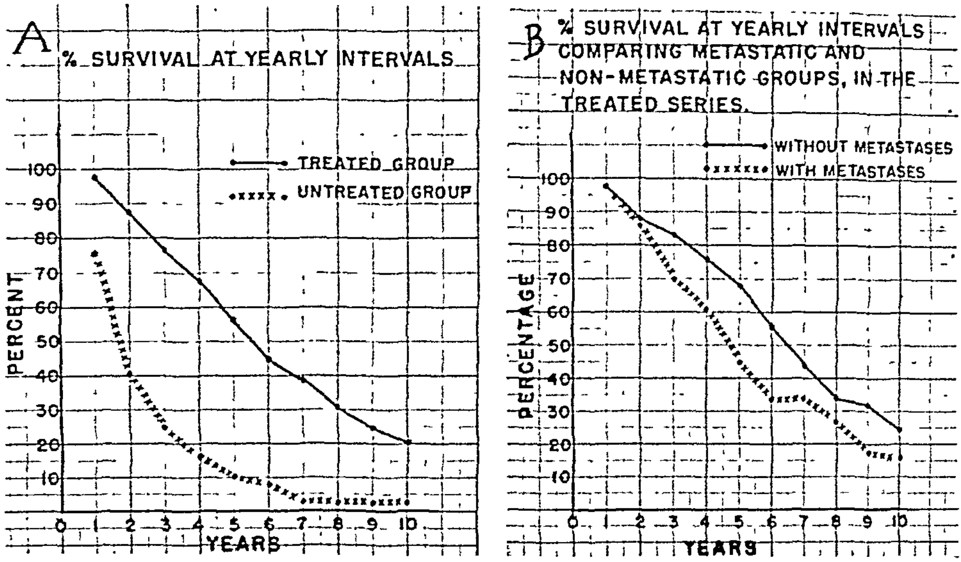

FIG. 3

There is no accurate method of determining the exact time the carcinoma begins in the prostate. Many of the cases were under treatment before a biopsy was obtained. It was quite definite clinically that the disease existed before obtaining the biopsy in many of these patients. Therefore, to use the date of biopsy as the onset in measuring longevity would be misleading. The authors are of the opinion that the disease existed in many cases even before symptomatology. It was therefore decided that the onset of symptoms should be the beginning of longevity, and we have based the survival rate from this point.

Eighty-five cases receiving some form of androgen control therapy were classified into three groups, determined by the type of therapy given; namely, a) stilbestrol alone, b) orchiectomy alone, c) orchiectomy and stilbestrol. The average survival rates in each group are shown in figure 2.

Group a, 23 cases without metastasis survived an average of 70 months; 9 cases with metastasis survived an average of 65 months.

Group b, 2 cases without metastasis survived an average of 75 months; 10 cases with metastasis survived an average of 54 months.

Group c, 16 cases without metastasis survived an average of 88 months; 25 cases with metastasis survived an average of 65 months.

Untreated group, 14 cases without metastasis survived an average of 18.9 months; 23 cases with metastasis survived an average of 37 months.

Twelve treated patients who lived 5 or more years died of causes other than carcinoma of the prostate. Of the 122 cases, 21 or 17.21 per cent died of causes other than carcinoma of the prostate. In the treated series of 85 cases, 16 or 18.82 per cent died of diseases other than carcinoma of the prostate.

Figure 3, *A* shows the percentage survival of the androgen control group and the untreated cases for a ten year period. The androgen control group had a five year survival of 56.47 per cent. The untreated group survival was 10.81

per cent. The androgen control group had a 10 year survival of 20 per cent; the untreated group was 2.7 per cent.

Figure 3, *B* shows that the 5-year survival of the androgen control group with metastasis was 45.45 per cent; of those without metastasis, it was 68.29 per cent. The 10-year survival of the androgen control group with metastasis was 15.90 per cent; of those without metastasis, it was 24.39 per cent.

CONCLUSIONS

The greatest incidence of this disease was found in the 60 to 80 year age group, the average age being 67.56 years.

The predominant symptoms were frequency, nocturia, and pain.

Adenocarcinoma was the most common pathological type and responded best to androgen-control therapy.

Acid phosphatase levels were elevated in 47 cases or 38.52 per cent and normal in 63 cases or 51.63 per cent when first seen. Twelve or 9.84 per cent had no acid phosphatase determinations. It was significantly reduced by androgen-control therapy in 26 or 36.6 per cent of the 71 cases followed by serial acid phosphatase determinations.

Cases treated by androgen control methods had a 5-year survival of 56.47 per cent and a 10-year survival of 20 per cent. This was compared to the untreated cases with a 5-year survival of 10.81 per cent and a 10-year survival of 2.7 per cent.

The results of this study showed that the combined use of estrogens and orchiectomy gives the greatest survival rates. The authors are of the opinion that estrogens and orchiectomy used together initially is the treatment of choice.

SUMMARY

One hundred twenty-two cases of histologically proven carcinoma of the prostate studied over a 10-year period are presented.

Eighty-five were treated with some form of androgen-control therapy.

Thirty-seven were treated well before 1941 and received no form of specific therapy.

An attempt has been made to show the five and ten year results of the various types of androgen-control therapy.

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SPERMATIC CORD TUMORS: REVIEW OF LITERATURE AND A CASE OF AN UNUSUAL VAS DEFERENS TUMOR IN AN INFERTILITY PROBLEM

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Extratesticular scrotal tumors are very rare. Not one report of a primary, benign epithelial tumor of the vas deferens could be found in the literature. According to the classification of Hinman and Gibson,[1] 90 per cent of extratesticular neoplasms in the scrotum occur in the spermatic cord. Thompson[2] states that most of these are lipomas and other benign lesions, but that a 30 per cent rate of malignancy is found. These cancerous tumors are almost exclusively of mesodermal origin.

Hinman, in 1926, and Thompson, in 1936, began the review of the literature. They brought the total of spermatic cord tumors to 242. Schulte, McDonald and Priestley,[3] in 1939, had reviewed nine more, and three years later Strong[4] added 14 cases. The list was carefully corrected in 1952 by Fitzpatrick[5] who, by adding two of his own cases, could bring the total to 286 reports.

Our own search has attempted to bring the published count up to date again. In 1951, Zuckner and Aronberg[6] reported a leiomyoma, and Ormond and Culp[7] added two lymphangiomas. Hashemian[8] submitted a lipoma in 1952, and Sherwin and Bergman[9] a leiomyosarcoma. Adding these recent five, plus one of our own, brings the total to 292.

CASE REPORT

A 26 year old married white man entered Wesley Memorial Hospital in August 1953 for the study of an infertility problem. Prior to admission, examination of a semen specimen had revealed oligospermia. Three months before this he had noticed a small mass in the scrotum. This was painless and had not changed in size. There were no other symptoms referable to the genito-urinary tract.

A review of symptoms by systems was negative. He had had mumps at age of eight, but no testicular involvement occurred. He was allergic to penicillin and sulfa drugs. Other than tonsillectomy, no operations had been performed. Physical examination was normal except for a small mass palpable in the right spermatic cord and attached to the vas deferens. It measured 0.5 cm. in diameter, was freely

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[1] Hinman, F. and Gibson, T. E.: Arch. Surg., **8:** 100, 1924.

[2] Thompson, G. J.: Surg. Gynec. and Obst., **62:** 712, 1936.

[3] Schulte, T. L., McDonald, T. R. and Priestley, J. T.: J.A.M.A., **112:** 2405, 1939.

[4] Strong, G. H.: J. Urol., **48:** 527, 1942.

[5] Fitzpatrick, R. J., Orr, L. M., Glanton, J. B. and Hayward, J. C.: J.A.M.A., **148:** 259, 1952.

[6] Zuckner, J. and Aronberg, L. M.: J. Urol., **66:** 285, 1951.

[7] Ormond, J. K. and Culp, O. S.: J. Urol., **65:** 906, 1951.

[8] Hashemian, H. A.: Brit. J. Urol., **24:** 2, 1952.

[9] Sherwin, B. and Bergman, H.: J. Urol., **67:** 208, 1952.

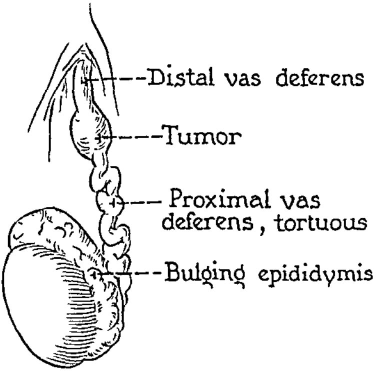

FIG. 1. Diagrammatic figure of tumor in situ

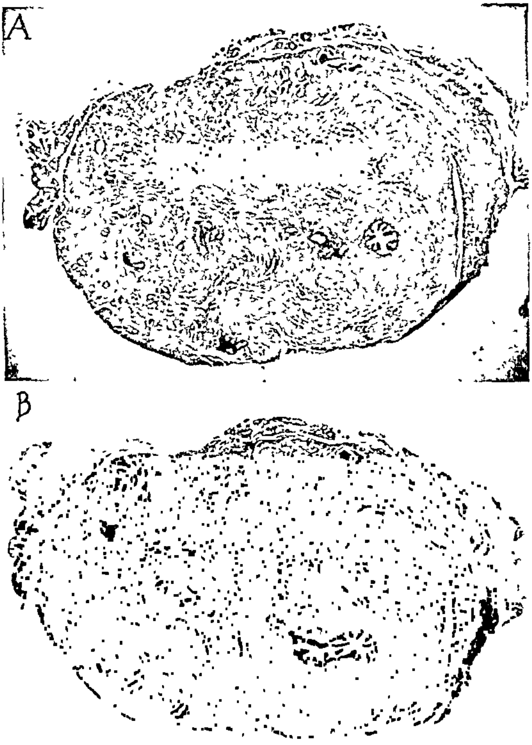

FIG. 2. A, showing entire tumor in section. *B*, showing continuity between lumen of vas and acini of tumor, several sections deeper.

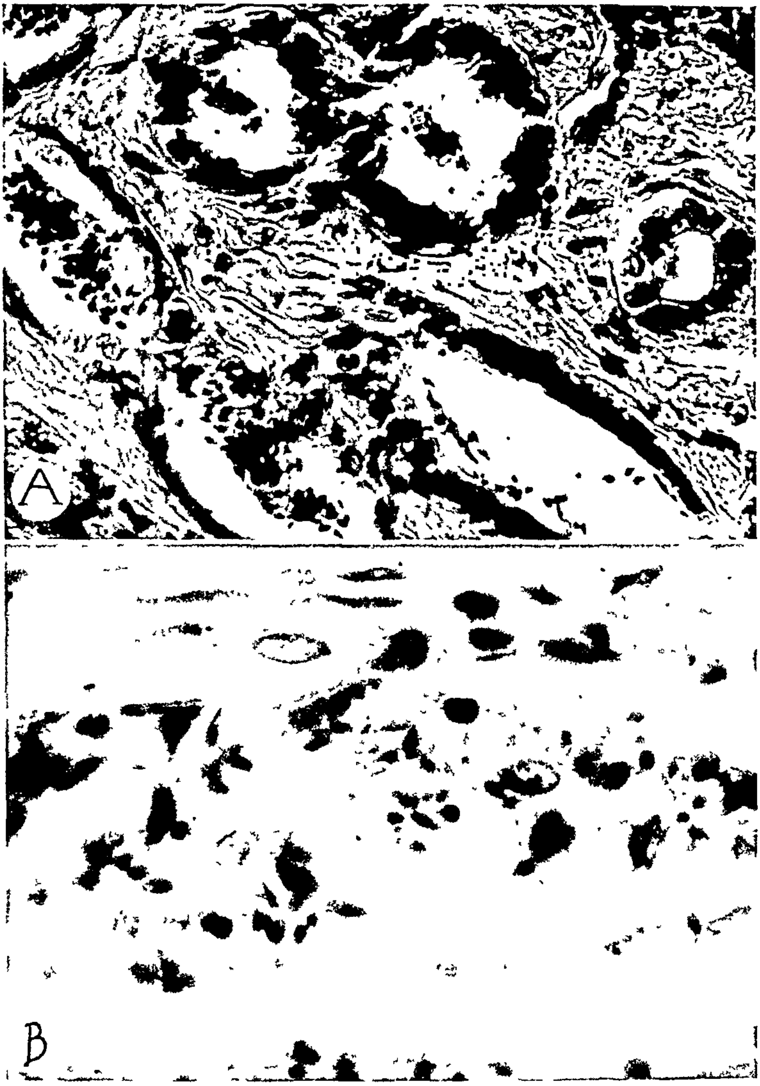

Fig. 3. *A*, showing detail of acini and stroma. *B*, oil immersion showing epithelium of one gland and spermatozoa in lumen.

movable, nontender, firm and smooth. The right testis felt normal. The left testis was atrophic and a moderate sized varicocele was found. The routine laboratory work, including serology, was normal.

At surgery, the mass was found to lie in the right vas deferens (fig. 1). The vas near the testis was noticeably dilated, as were the convolutions of the epididymis. The right testis was normal.

A segmental resection of the portion of the vas bearing the tumor was then done by Dr. O'Conor. A semen specimen from the proximal cut end of the vas was examined microscopically and found to contain sperm in large numbers with good morphology and motility. The lumen of the tumor would not admit a thin probe. Re-anastomosis of the vas over silkworm gut splint using 6-0 stainless steel sutures was then performed.

One month postoperatively, office semen analysis showed a definite improvement in the sperm count.

Pathologic description by Drs. T. C. Laipply and J. T. Sherrick was as follows: "Grossly, the specimen is a crescentic shaped piece of moderately firm, pale tan tissue measuring 1.8 by 0.4 cm. At one end a duct-like structure is visible on sectioning. This has a pin-point lumen in some sections.

"Microscopically, multiple sections reveal vas deferens. The mucosal layer is pseudostratified columnar epithelium thrown into papillary folds with an underlying lamina propria of fibrous connective tissue. Surrounding this layer is dense fibromuscular tissue within which are many glandular structures. Spermatozoa are seen within the lumina of these glands. The acini are oval and elongated and lined by tall columnar and low cuboidal epithelium with oval, basophilic nuclei. Serial sectioning reveals communication between the lumen proper of the vas and the larger tubular divisions of the glandular network. The diagnosis is ductal hyperplasia of the vas deferens." See figures 2 and 3.

DISCUSSION

In this case, an obstruction to the outflow of sperm was present in the right vas deferens at the site of a tumor. This, together with an atrophy of the left testis, had caused oligospermia. Serial sectioning of the tumor showed the lumen to resolve itself into a fibromuscular stroma containing glands. It might be postulated that ductal hyperplasia at the site of an atretic lumen formed the glands However, ectopic mesonephric duct tissue can occur in this vicinity; in fact, Dr. L. B. Arey of Northwestern University Medical School thought the tumor resembled rete testis. Dr. M. C. Wheelock of the Northwestern Department of Pathology made the diagnosis of adenomatoid tumor. This entity has been reported in the epididymis by Codnere and Flynn[10] and in the genitalia of both sexes by Golden and Ash.[11] Some authors favor a mesonephric origin for adenomatoid tumors.

The close resemblance of this tumor to the gynecological lesion called "salpingitis isthmica nodosa" has been noted. Here, an inflammatory rather than a congenital or neoplastic cause is implicated.

SUMMARY AND CONCLUSIONS

Tumors of the spermatic cord are rare. The total in 1952 was 286; we have found five more reports and added one of our own, bringing the total to 292. Our lesion represents a growth originating in the epithelium of the vas deferens, possibly at the site of an atresia. We were unable to find a similar report in the literature. The obstruction of the vas on the right side, plus testicular atrophy on the left, had caused oligospermia. Re-anastomosis, after segmental excision of the tumor, has resulted in an improved sperm count.

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[10] Codnere, J. T. and Flynn, J. E.: J. Urol., 56: 448, 1946.

[11] Golden, A. and Ash, J. E.: Am. J. Pathol., 21: 63, 1945.

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TREATMENT OF GENITO-URINARY TUBERCULOSIS

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This paper is based on a study of 27 cases of genito-urinary tuberculosis which have been under the surveillance of the urological staff of Shaughnessy Hospital since 1947. The series is not a large one, but it happens to compare numerically with the few series being reported in the current literature and is perhaps unique in one respect, that we are able to report 100 per cent follow-ups 5 years after the diagnoses were established. All but two of our patients were under the age of 35.

INCIDENCE OF ORGAN INVOLVEMENT

It is apparent from figure 1 that the majority of cases showed involvement of epididymis (almost 50 per cent). In order of frequency, the kidney, the bladder, and the prostate were involved.

They add up to more than 100 per cent and it is apparent that there must be considerable overlapping; in other words, genito-urinary tuberculosis in most instances involves more than one organ in the tract. Indeed, in our series, only 2 cases have so far shown involvement of only one organ. In the face of this finding, one might doubt the merits of surgical removal of a single organ, such as the epididymis or kidney, in the expectation that a cure will ensue to the patient. Statistically, the patient has tuberculosis elsewhere in the genito-urinary tract. The incidence of extra-urogenital tuberculosis in our series is perhaps best illustrated in figure 2.

Half our cases are known to have tuberculosis of the lungs and some have bone and lymph node involvement. To this date 12 cases have shown no signs or sumptoms of tuberculosis outside the genito-urinary tract.

THE PRESENTING SYMPTOMS AND DIAGNOSTIC METHODS UTILIZED

Swollen testicle. With what symptoms did these patients present themselves? See table 1. It warrants repetition that almost half our patients presented themselves with swelling of the scrotum due to tuberculous epididymitis. These cases present no insurmountable problem in diagnosis; the onset is insidious rather than acute, usually unilateral, and not preceded by injury or venereal disease. The patient complains of an aching, but not especially tender scrotum, which he has noted for some period of time (days or weeks). He probably denies any urinary disturbances. In the early stages, nodularity of the epididymis is absent and by palpation one cannot differentiate it from chronic nonspecific epididymitis. A trial of penicillin or sulfa therapy usually produces a favorable response in the nonspecific infection, and no response if the condition is tuberculous. Positive urine cultures for tuberculosis will be found in the majority of cases but diagnosis cannot be established accurately without surgical excision of the epididymis.

Read at a meeting of the British Columbia Surgical Society, April 30, 1952.

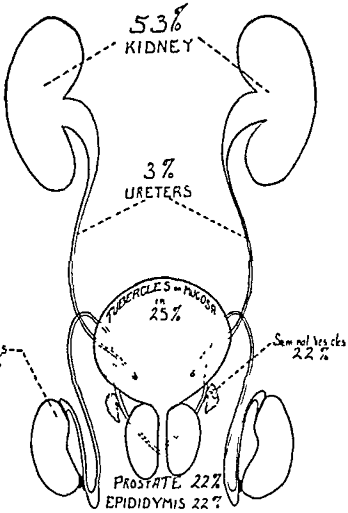

FIG. 1

Frequency. This is a very common urinary complaint. When it persists in a young person in spite of treatment, tuberculosis must be ruled out. One of our patients suffered this symptom continuously for 4 years before renal tuberculosis was suspected.

Nocturia. This is an uncommon symptom in the young person. Its persistence should be a clue to the clinician in the diagnosis of genito-urinary tuberculosis.

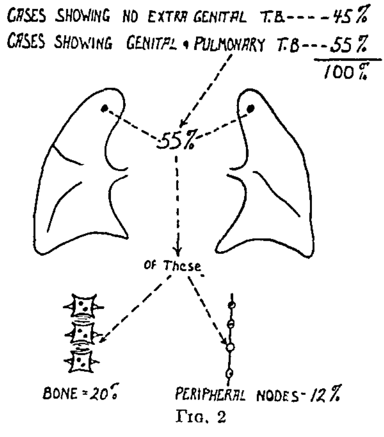
CASES SHOWING NO EXTRA GENITAL T.B.----45%
CASES SHOWING GENITAL + PULMONARY T.B---55%
100%
55%
Of These
BONE = 20%
PERIPHERAL NODES - 12%

FIG. 2

TABLE 1

Sign or Symptom	No. Cases	Per cent
Swollen testicle	13	50
Frequency	3	8
Nocturia	2	8
Urethritis (nonspecific)	2	8
Albuminuria	2	8
Pyuria	2	4
Pain in back	1	4
Hydrocele	1	4
Routine T.B. culture (because of bone tuberculosis)	1	6
	27	100

Urethritis. Tuberculous urethritis did not occur in this particular series. However, after 2 patients with nonspecific urethritis were rendered free of their urethral discharge by routine therapy, the associated frequency, nocturia, and occasional dysuria persisted and only after repeated monthly cultures were taken over a period of 6 months was a diagnosis of urinary tuberculosis made. The necessity for repeated and repeated urine cultures for tuberculosis cannot be over-emphasized.

Albuminuria. The causes of albuminuria are legion. The etiological factor in the first of our cases was determined by a routine excretory urogram. The second case, however, showed no radiological changes on excretory urography. The third urine culture from the right ureter of this second case was our first proof of tuberculosis. The diagnosis in this particular case was established in March 1947, and we have not as yet removed this kidney.

Pyuria. Pus in an acid urine is almost pathognomonic of genito-urinary tuberculosis. These patients were referred to us only because the pyuria failed to respond to usual chemotherapeutic agents.

Pain in the back. Renal tuberculosis may present itself with obscure pain in the back. Realizing this, the Orthopedic Department at Shaughnessy Hospital unmasked 3 cases of genito-urinary tuberculosis out of 45 patients under treatment for tuberculous disease of bone. Because of this incidence, one would presume to recommend to those who treat tuberculosis of bone, that urine cultures for tuberculosis should be done monthly and repeatedly. Only two of our cases are included in this particular series, the others having been detected after this series was started in 1947.

SURGICAL TREATMENT

Four surgical procedures are recommended in the treatment of this disease: 1) epididymectomy; 2) nephro-ureterectomy; 3) prostato-seminal vesiculectomy; 4) heminephrectomy.

Epididymectomy. See figure 3. Having established the diagnosis of tuberculous epididymitis or having suspected it with reasonable justification, the surgeon should excise the epididymis as high as possible without going through the ab-

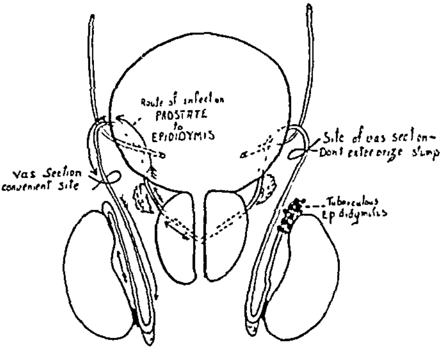

FIG. 3

dominal wall. The stump of the vas need no longer be exteriorized, thanks to streptomycin. If the pathologist confirms the diagnosis, a vas section on the other side should be carried out. The rationale of this procedure is apparent if one considers the common route of infection from the prostate through the vas to the epididymis. Thirteen epididymectomies were performed in this series; three were bilateral, presumably due to failure to perform contralateral vas section at the time of the initial epididymectomy (table 2). In only 2 cases was the tuberculous activity confined to the epididymis. The other eleven, or 85 per cent, were proved to have tuberculosis elsewhere in the body. Besides the group showing concomitant involvement of lungs, kidneys, and bone, six were later proved to have tuberculous prostatitis. In view of these facts, surgical removal of local lesions only would have produced favorable results in only 15 per cent.

Nephro-ureterectomy. In our opinion, if renal destruction is indicated by x-ray, as in figure 4, in the presence of positive urine culture, nephro-ureterectomy is indicated. On the other hand, tuberculous bacilluria alone, without radiological evidence of kidney damage, does not justify the immediate removal of the organ. Can the tubercle bacillus pass through the kidney without producing a renal lesion? Most pathologists say no. However, two kidneys were removed on the strength of repeated positive cultures from corresponding ureters and when examined in serial section the pathologists were quite unable to demonstrate even the tiniest tuberculous lesion.

TABLE 2. *Lesions associated with epididymitis*

Cases	%	Lung	Renal	Bone	Nil
4	35	3	—	—	—
5	38	—	5	—	—
2	12	—	—	2	—
2	15	—	—	—	—
13					

A 26-year old man showed positive urine cultures from the right kidney five years ago. The bilateral retrograde pyelogram is shown in figure 5. He was treated with streptomycin and sanitarial routine only. There has been neither radiological nor other evidence of tuberculous activity since that time. In the days prior to streptomycin and modern sanitarial regimentation, isolation of the bacillus from one kidney meant mandatory nephrectomy. Today we elect to await radiological evidence of renal destruction or response to therapy before sacrificing the organ. However, if repeated urine cultures remain positive while the patient is on streptomycin, or become positive immediately after the cessation of the drug, then we think nephrectomy is indicated in spite of negative radiological findings. See figure 6.

Tubercles were isolated from the left kidney only. The x-ray did not appear abnormal. While on streptomycin, his urine was negative, but four weeks after cessation of the drug, cultures were positive again. Repeated x-rays (fig. 6, *B*) show no evidence of renal damage. These x-rays (fig. 6, *A* and *B*) were taken 12 months apart. After 18 months of repeated courses of streptomycin, the urine remained positive and in the face of these negative x-ray findings, contrary to our custom, the kidney was removed, which showed the large renal lesion (fig. 6, *C*). A further lesson concerning the fallibility of x-ray in diagnosing tuberculosis might be learned from this.

Prostato-seminal vesiculectomy. Prostato-seminal vesiculectomy is a radical procedure and a very serious one when performed on a young patient, for the invariable impotence that follows is permanent and complete. However, sometimes it is a life-saving procedure.

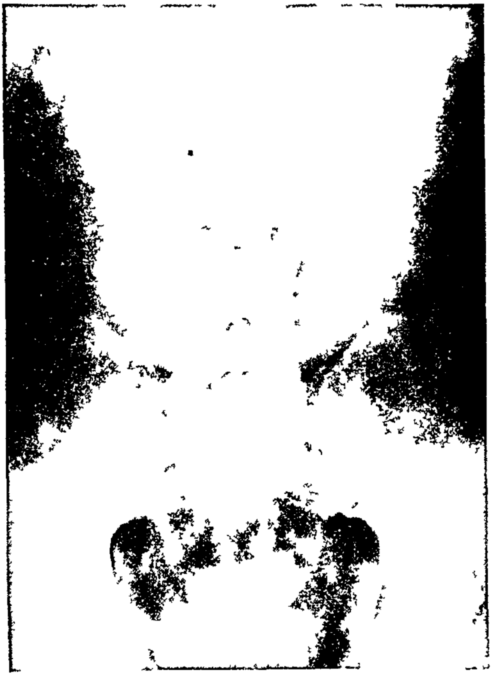

FIG 4

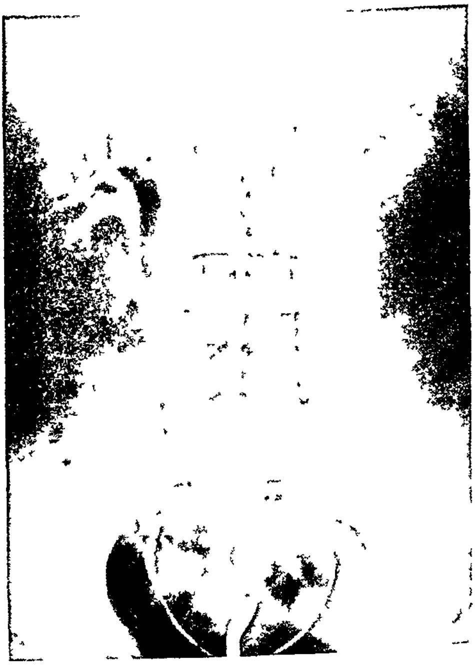

FIG. 5

In the case illustrated by figure 7, the pool of infection was located in the prostate. For 18 months the prostatitis was not identified as tuberculous. From time to time he exhibited frequency and dysuria and vague pain in the right lower quadrant which appendectomy failed to ameliorate. Right nephrectomy was performed and a small, early tuberculous lesion was found in the upper pole. His

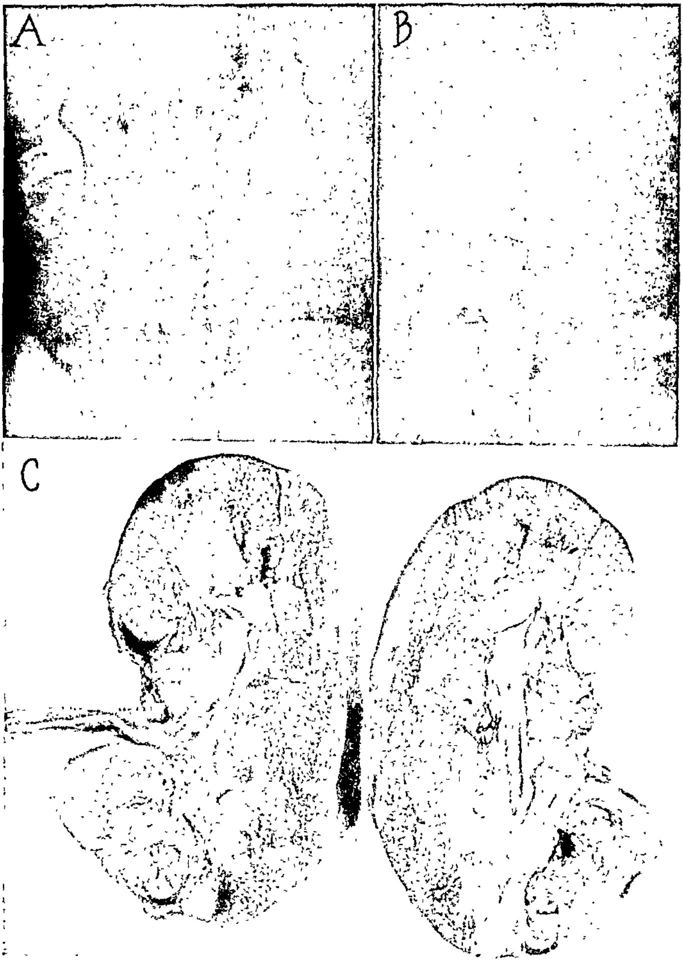

FIG. 6

TABLE 1. *Vital statistics of patients under treatment*

Patient	Age	Diagnoses	Treatment with Furadantin		
			Days of treatment	Dose	
				Total (gm.)	Mg./kg/24 hrs.
G. B. J.	30	Lithiasis Pyelonephritis	7	5.25	9.9
O. E. S.	32	Chronic cystitis	7	3.15	6.1
L. S. G.	41	Lithiasis Pyelonephritis	7	3.15	6.5
M. G.	25	Hydronephrosis (postobstructive)	7	3.15	6.6
L. G. M.	38	Cystitis cystica	7	3.15	6.0
O. M.	25	Hydronephrosis (postobstructive)	7	3.15	6.5
S. N.	52	Chronic pyelonephritis	7	3.15	6.5
W. S.	24	Paraplegic Urethrocutaneous fistula Chronic cystitis	7	3.15	6.5

percentage of control (D/C × 100) in tables 2 and 3. Before treatment, the patients presented no evidence of severe impairment of renal function as measured by GFR except for one patient (S. B. N.). There was no significant change in renal hemodynamics, tubular function, or the excretion of water, sodium, or potassium in the first seven patients studied (average, A), but one patient (W. L. S.), who demonstrated moderate impairment of renal function in the control state, showed a marked improvement in the discrete renal functions after therapy.

TABLE 2. *The effect of furadantin therapy for seven days on renal hemodynamics*

Patient	Glomerular Filtration Rate						Renal Plasma Flow			Filtration Fraction $\times 10^2$			Renal Blood Flow		
	Clearance of Inulin (ml/min)			Clearance of Creatinine (ml/min)			Clearance of PAH (ml/min)			GFR/RPF			(ml/min)		
	C	D	D/C	C	D	D/C	C	D	D/C	C	D	D/C	C	D	D/C
G. B. J.	105	110	105	119	122	103	864	847	98	12	13	108	1465	1396	95
O. E. S.	106	108	102	132	111	84	864	929	108	12	12	100	1489	1583	106
L. S. G.	108	106	98	95	72	76	834	767	92	13	14	108	1596	1470	92
M. G.	83	95	114	102	97	92	620	875	141	13	11	85	1159	1593	131
L. G. M.	123	113	92	151	130	86	1239	1760	142	10	6	60	2213	3099	140
O. M.	107	104	97	126			885	884	100	12	12	100	1608	1579	98
S. N.	58	62	107	78	74	95	466	435	93	12	14	117	804	676	84
W. S.	89	141	159	67	105	157	358	993	277	25	14	56	672	1839	274
Average A	97	100	102	115	101	89	825	928	111	12	12	97	1476	1628	107
Average B	96	105	109	109	101	99	766	936	131	14	12	92	1375	1654	131

C = Control D = on seventh day of therapy D/C × 100 = % of control

TABLE 3 *Effect of furadantin therapy for seven days on renal tubular function and excretion of water, sodium and potassium*

Patient	Maximum Tubular Excretory Capacity (TmPAH) (mg/min)			GFR/TmPAH			Urine Volume (ml/min)			Na Excretion (microEq/min)			K Excretion (microEq/min)		
	C	D	D/C	C	D	D/C	C	D	D/C	C	D	D/C	C	D	D/C
G B J	103	116	113	102	95	93	15	12	80	90	78	87	66	51	77
O E S	126	120	95	84	90	107	8	9	113	92	115	125	80	89	111
L S G	112	110	98	97	96	99	14	15	107	173	130	75	68	70	59
M G	107	107	100	78	89	114	7	9	129	77	112	145	81	59	73
L G M	102	133	130	121	85	75	12	9	75	232	165	71	79	77	97
O M	90	85	94	119	122	103	14	16	114	217	138	64	101	131	130
S N	65	72	111	89	86	97	6	3	50	102	204	200	42	55	131
W S	89	116	130	100	122	122	12	19	158	160	154	96	39	36	92
Average A	101	106	106	99	95	98	11	10	96	129	135	110	71	72	97
Average B	99	107	109	99	98	101	11	9	103	133	137	108	70	67	96

C = Control D = on seventh day of therapy D/C × 100 = % of control

TABLE 4 *The effect of furadantin therapy for seven days on hepatic function*

Patient	Cephalin Cholesterol Flocculation		Thymol Turbidity (MacLaglen Units)		Alkaline Phosphatase (K A Units)		Prothrombin Time (% of normal)		Bilirubin (mg %)	
	C	D	C	D	C	D	C	D	C	D
G B J	0	0	2	1	4	—	90	75	0 5	0 6
O E S	0	0	2	3	—	—	100	100	0 7	0 4
L S G	0	0	2	2	3 7	2 9	—	—	0 5	0 4
M G	0	0	2	2	—	—	95	100	0 5	0 5
L G M										
O M	0	0	1	1	1 5	—	—	—	0 5	0 3
S N	0	0	1	1	3 0	3 0	100	—	0 4	0 4
W. S										

TABLE 5 *The effect of furadantin therapy for seven days on bacteriologic culture of the urine*

Patient	Urine Culture	
	Before treatment	After completion of 7 days of treatment
G B J	Gram negative rod	Gram negative rod
O E S	Pseudomonas	Pseudomonas
L S G	Pseudomonas	Pseudomonas
M G	Pseudomonas	Pseudomonas
L G M	Staphylococcus aureus	No growth
O M	Alkaligenes	Alkaligenes
	Pseudomonas	Pseudomonas
S N	Pseudomonas	Pseudomonas
W S	Proteus vulgaris	Proteus vulgaris

There was no change in the excretion of sodium and potassium in this patient however. If this patient is included in the overall averages, there will be a slightly higher "apparent improvement" in the functions after therapy (average, B), but it is to be noted that none of the changes are significant.

B. Hepatic effects. There was no change in liver function during furadantin therapy as measured by clinical liver function tests (table 4).

C. Urine bacteriology. One patient (L. G. M.), who demonstrated Staphylococcus aureus on urine culture prior to therapy, was bacteriologically negative after 7 days of furadantin. The other 7 patients showed no change in the urine culture on the last day of furadantin therapy. *In vitro* sensitivity tests for the particular organisms were not done (table 5).

CONCLUSIONS

Furadantin used in the treatment of urinary infections at the dosages (less than 10 mg./kg./24 hours) and duration (under 8 days) recommended appears to be free from harm to kidney and liver. In the present short-term study, there was no effect on urine bacteriology in seven out of eight patients.

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IMPORTANCE OF VAGINITIS IN URINARY INFECTIONS OF CHILDHOOD

RAYMOND STEPT

In the past few years, chronic urethritis in girls has been recognized as one of the most common causes of urinary infection in childhood. It is surprising that an entity of such frequent occurrence should have been ignored for so many years. Some urological textbooks do not even note its existence or, at best, mention it so briefly that students complete their medical education with total unawareness of the condition, and are completely baffled when it first presents itself. Unfortunately, too, we have reason to conclude that many urologists and pediatricians are not sufficiently aware of its manifestations, as indicated by the many patients who go from physician to physician before receiving proper management. In our experience, and the experience of others,[1] urethritis in young girls is among the most common causes of urinary complaints in pediatric Urology. Furthermore, there are many more unhappy patients who never reach the urologist at all because their complaints are not strengthened by the finding of pus in the urine, and so are not considered seriously.

Ordinarily, chronic urethritis can be satisfactorily treated by means of urethral dilations supplemented by various medications to eliminate the urinary infection.[2] However, a significant group of patients who do not respond to simple management have come under our care, and it is in this group that the control *of accompanying nonspecific vaginitis has been so vital to successful treatment.* Whether or not the advent of the antibiotics has increased its incidence remains to be observed. Search of the current and older literature, with few exceptions, places little emphasis on nonspecific vaginal discharges of childhood. It is true that not all little girls who have vaginal discharge have urinary complaints or, indeed, any complaints at all. However, when vaginitis co-exists with urinary infection, no more than temporary relief of the urinary symptoms can be expected until it is eradicated. It is in reference to this particular group of patients that this presentation is given.

MATERIALS

This series consists of 15 patients observed in private practice in the past 3 years who had recurrent episodes of urethritis, with or without pyuria, despite the usual treatment, none of whom could be satisfactorily controlled until the vaginal infection was cleared up. Six of these patients had had complete urological study and treatment by competent urologists elsewhere. In addition, in three of the six patients, gynecological consultants had not recognized the significance of obvious vaginal irritation. These children ranged in age from 26 months to 11 years, with an average age of 5 years. Symptoms had been present

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Read at annual meeting of Northeastern Section of American Urological Association, Shawnee-on-the-Delaware, September 17, 1953.

[1] Hodges, C. V.: Chronic urethritis in girls. J. A. M. A., **149:** 753–757, 1952.

[2] Roen, P. R. and Stept, R.: Urethritis in girls. Am. J. Dis. Child., **72:** 529–535, 1946.

for at least 6 months in eleven of the 15 patients, and in four instances the mother stated that symptoms had been present since infancy. Most patients were hospitalized for complete urological study which included routine blood count and examination of the catheterized urine, visualization of the bladder and urethra with the McCarthy miniature cystoscope, smears and cultures of the urine and vaginal secretion and, in a few instances, vaginoscopy. Residual urine was not present in any of these patients.

SUBJECTIVE AND OBJECTIVE FINDINGS

The symptoms of urethritis are well known. Urgency, dysuria, nocturia and diurnal frequency are the most characteristic complaints. Hematuria and obstructive symptoms are unusual but may occur.[2] There is often a history of numerous episodes of less than 48 hours' duration subsiding spontaneously without interval complaints. Fever is not present until ascending infection supervenes.

The urinary findings can ordinarily be consistently interpreted with relation to the vaginal infection. Whereas, in uncomplicated urethritis, the urine will be normal between attacks, or even during acute attacks, when vaginitis is present the findings will frequently be so characteristic that the presence of vaginitis can be anticipated. Even when there are as few as 1 or 2 white blood cells/high power field, one will often find numerous bacteria and yeast cells in the urine. Even after suitable treatment of an episode of severe pyuria, although the white blood cells will have disappeared from the urine, the yeast cells may persist for days or weeks, until such time as the vaginitis has cleared up. Conversely, in the follow-up of these patients, it is commonly observed that the yeast cells will precede the recurrence of pyuria and urinary complaints by days or weeks. As we shall note later, this can serve as a useful guide to therapy directed to the vagina. It must be emphasized, however, that the yeast cells are not to be construed as the cause of the infection because they are so commonly present, but rather interpreted as a co-incidental finding as the result of spillage of vaginal secretions into the urethral orifice. In short, when this secretion can gain entrance into the urinary tract, urinary infection will ultimately ensue. Fortunately, in many patients with vaginal infection, for some reason the secretions do not invade the urethra.

The gross appearance of the external genitalia is easily apparent. In almost every instance the hymen has been widely patent and examination easily done. There is a slight to moderate amount of vaginal discharge which is usually thin and serous, but may be mucoid. Although the vaginal mucosa may be pale, there is definite redness of varying degrees of the introitus extending over to the region of the urethral meatus. Indeed, it is logical to interpret the urethral changes as a mere extension of external inflammatory changes. The labia, too, are characterized by varying degrees of irritation and redness, and this frequently extends over to the inner thigh where a sharply demarcated area of chafing is seen. In the subacute and chronic phases, the changes over the labia are less striking in degree, but careful inspection will reveal thickening and superficial desquamation of the skin. However, even with minimal changes externally, separation of the labia will disclose the striking congestion surrounding the urethral meatus, and the excessive vaginal secretion.

Cultures of the vaginal secretion and urine may be noteworthy. Urine cultures may be sterile, but often contain the bacterial offenders ordinarily found in urinary infections, especially E. coli, B. proteus, and beta hemolytic Staph. aureus. When pyuria is present, the same organism can usually be isolated from both the vagina and urine, emphasizing their relationship. In three patients a significant bacteriological phenomenon was noted: a beta hemolytic Staph. aureus which was coagulase negative in the vagina was found to be coagulase positive in the urine, indicating that the pathogen had probably existed in an attenuated state in the vagina before invading the urinary tract. The behavior of the yeast cells was especially puzzling. Even when seen in wet smears of the freshly collected urine, or on stained smears from the urine or vagina, they could not be grown on either routine culture media or specialized media ordinarily used for yeast cultures. The yeast cells morphologically appear to be young forms of Candida albicans, occurring singly, in clusters, and in chain formation, but in view of the cultural problems encountered, their identity cannot be stated with any degree of certainty.

The cystoscopic findings have been described elsewhere and need not be repeated here. They are not unlike those observed in the adult. Vaginoscopy, accomplished with either the open air urethroscope or panendoscope, does not yield remarkable results. Despite excessive vaginal secretion, the vaginal mucosa is usually pale and smooth and the cervix normal, and only occasionally does one find mucosal congestion or patchy hypervascularity. The appearance of the introitus, however, is much more striking than the vaginal canal itself so that vaginoscopy is not now employed routinely.

It should be emphasized that cystoscopy and vaginoscopy are always performed under general anesthesia, either rectal pentothal or avertin supplemented by an inhalation agent.

TREATMENT

Proper therapy has a threefold objective: 1) eradication of the pyuria, if present, 2) treatment of the urethritis, and 3) control of the vaginitis. The urinary infection is ordinarily controlled easily by the use of a sulfonamide preparation, or such antibiotics as aureomycin or terramycin. Penicillin and streptomycin have not been necessary in any instance. Local bladder instillations of silver preparations, antiseptic agents, or antibiotic solutions have not been necessary for systemic medication always clears up the initial pyuria if organic obstruction is not present.

Urethral dilation for the urethritis is initiated while the child is under anesthesia for cystoscopy. Urethral stenosis will be encountered in a significant number of patients, but the urethra is dilated whether narrowing is present or not. The relief experienced may be rapid and dramatic, probably due to relaxation of bladder neck spasm incident to the urethral irritation. Several urethral dilations are given at seven to ten day intervals, until a 20F sound can be passed easily. Fulguration of the urethra has not been required in any instance.

Control of the vaginitis by local treatment is the *sine qua non* to the prevention of relapse and recurrence. This phase of therapy may be prolonged and may severely tax the patience of both physician and parents. It must be viewed as a form of maintenance therapy, as in any type of recurring illness, and if this attitude is not adopted, discouragement and failure will surely follow.

The following regimen of local therapy has been most efficacious: the vagina is treated by the application of polymyxin B sulfate ointment, or sulfa jelly or cream directly into the vaginal canal, an excess being applied over the introitus and labia. In the acute phase applications are made nightly, then the interval is reduced to three times weekly, then twice weekly until ultimately maintenance treatment as required in the individual patient is determined. In some patients treatment can be stopped completely within a month; in others, vaginal medication at two-week to two-month intervals has been required. Observation of the urine at intervals is an excellent guide to treatment: when the urine is microscopically free of all abnormal elements, it will usually be found that the vagina appears healthy and the patient has been asymptomatic. Interestingly, it has been observed that when epithelial cells and yeast cells appear in the urine, despite the absence of pus cells, the vagina has begun to appear reddened, and urinary symptoms as well as pyuria will probably recur soon if the vagina is not treated. If followed patiently and carefully, most patients will clear up within a few months, but there are a resistant few who require even longer supervision. None of these patients has been followed into puberty as yet, but it is quite possible that the normal physiological changes occurring at that time will spontaneously correct the situation by establishing a more acid vaginal pH.

Other agents employed were not so effective as polymyxin or sulfa jellies. Estrogen therapy employed in three patients both parenterally and by vaginal suppository was completely ineffective. Aureomycin and terramycin vaginal suppositories were so irritating that their use was not continued. Aci-jel, used in two patients, was slightly helpful. Sulfonamide vaginal inserts (tablet form) were difficult and painful to administer, and not productive of good results. Triple sulfa creams were effective in three patients.

Polymyxin was used both as polysporin ointment, a mixture with bacitracin, and as the pure polymyxin B sulfate ointment. The former was occasionally slightly irritating, but the latter was almost uniformly well tolerated. The ointment was packaged in tubes with a short nozzle which could easily be inserted into the vaginal opening or, when this type of tube was not available, a short plastic nozzle was adapted to the tube.

RESULTS

Control of the initial infection and recurrences was attained in all patients, although the time required varied greatly. The confirmed impression was gained that a successful outcome is assured in practically every patient if the mother is co-operative and persistent. In approximately one-half of these patients, complete cure was obtained within three months so that all treatment could be discontinued. In the remainder, maintenance care directed to the vagina alone has been necessary.

REPORTS OF ILLUSTRATIVE CASES

Case 1. S. M., aged 4½ years, was seen because of urgency, frequency and dysuria accompanied by severe pyuria and constant low grade fever since 2 years of age. The infection had consistently responded to sulfa preparations only to recur within 10 days after discontinuance of medication. Complete urological study disclosed typical chronic urethritis and evidence of vaginal hypersecretion. Dilations of the urethra resulted in moderate but incomplete improvement. Local and parenteral estrogen therapy did not influence the vaginal infection. Ultimately, a triple sulfa vaginal jelly was used with rapid control of the vaginitis. Since that time (two years ago), only maintenance therapy to the vagina has been used and there has been no recurrence of pyuria. Occasional episodes of urethral irritation have responded promptly to vaginal treatment alone.

Case 2. A. W., aged 5 years, had had urgency of urination since early infancy. Hematuria and dysuria began 48 hours before she was first seen. Complete urological study disclosed urethral stenosis and urethritis, and acute hemorrhagic cystitis. Treatment by urethral dilation, aureomycin, and gantrisin were helpful, but recurrences were frequent. Six months later typical nonspecific vaginitis was noted. Vaginal treatment with polymyxin ointment locally resulted in complete and permanent clearing of the urine and subsidence of all symptoms. Since that time (two years ago), no other treatment has been required.

Case 3. C. C., aged 3 years, had had frequent recurrences of pyuria and low grade fever since birth. There were no urinary complaints, but attacks of abdominal pain were frequent. Administration of antibiotics had been only temporarily helpful. Complete urological study revealed severe chronic urethritis and a low grade vaginitis. The urine was rendered normal with oral antibiotics plus a vaginal jelly, and was so maintained thereafter by vaginal medication alone. In almost two years there have been no recurrences of urinary infection and the patient's general health and disposition have been immeasurably improved.

COMMENT

Nonspecific vaginitis is a common occurrence, but is usually disregarded until the onset of symptoms makes treatment mandatory. Symptoms may be referable to the urinary tract or to the genitalia or to both. Many etiological factors have been mentioned, some of which do not appear important. The fundamental disturbance in the vagina appears to be a change in the activity of the vaginal mucosa which for some unexplained reason results in the excessive secretion of a discharge of such alkalinity or mild acidity that a favorable medium for bacterial growth is created.[3] Whereas, in the adult, vaginal secretions are of such acidity that bacterial pathogens are not encouraged, in the child the secretion is normally of a much higher pH and not unfavorable to many pathogens. With the infected vaginal secretion bathing the urethral meatus, it is only a matter of time until urethral irritation occurs, to be followed in due time by actual infection of the urinary tract.

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[3] Bernstine, J. B. and Rakoff, A. E.: Vaginal Infections, Infestations and Discharges. Philadelphia: P. Blakiston's and Son Co., 1953.

Many types of bacteria, both pathogenic and nonpathogenic, as well as yeast cells, have been seen, but these appear to be superimposed upon a previous vaginal hypersecretion rather than to be its cause. This observation has been made in the study of nonspecific vaginitis in the adult as well.[4] Foreign bodies in the vagina are of unusual occurrence. Masturbation is an important factor in the minds of many clinicians, but is probably the result of the vaginal irritation rather than its cause,[5] since this habit disappears when the vaginitis has been alleviated. Fecal contamination from the rectum is a common occurrence in all children, but it may well be that only those who have a previous excess of vaginal secretion will harbor the organisms normally found in the feces. The flare-up of vaginal and urinary complaints during or following an upper respiratory infection is common knowledge, and is especially interesting. Although this phenomenon is ordinarily attributed to a general lowering of bodily resistance, it is perhaps more plausible that the sympathetic turgescence and hypersecretion of the vaginal mucosa coinciding with the inflamed schneiderian membrane increases the vaginorrhea and encourages previously quiescent organisms to become active. The wearing of tight fitting panties can cause considerable irritation of the external genitalia, and certainly such a situation should be corrected, but again it is likely to offend only when an underlying vaginal disturbance is already present. The acute exanthemata are a frequent activator of vaginitis. General debility and malnutrition are important at times, though they were not encountered in this series. Hyperestrinism also has been mentioned as a possible cause of vaginal hypersecretion, but there has been no real clinical evidence to support this.

Ordinarily, no special techniques of examination are required to recognize the situation. Vaginoscopy is seldom necessary and in the presence of a normal upper urinary tract, as seen by excretory urography, the cystoscopic findings can almost be anticipated. It is only in resistant cases that instrumentation is mandatory.

SUMMARY

There are numerous instances of recurrent urinary infection in girls associated with urethritis in which the usual methods of treatment do not give lasting relief. Many of these patients have a nonspecific vaginitis resulting from vaginal hypersecretion. In addition to the usual measures, local treatment of the vagina, sometimes for long periods, is necessary. The condition may have its inception in infancy and persist until puberty. Vaginal treatment can practically always prevent the recurrence of urinary infection, and in association with other measures, offers the only chance for permanent cure. A regimen of therapy is described.

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[4] Weaver, J. D., Scott, S. and Williams, O. B.: The bacterial flora found in nonspecific vaginal disease. Am. J. Obst. & Gynec., 60: 880-884, 1950.

[5] Schauffler, G. C.: Pediatric Gynecology, 2nd ed. New York: Year Book Publishers, Inc., 1947.

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SALMONELLA URINARY TRACT INFECTION

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Salmonella are now recognized among the more important agents of infectious disease in the human. Recently special attention has been given these bacilli and three Salmonella centers have been established in the United States. The diseases caused by them used to be called paratyphoid fever, but, we now know that these organisms cause disease pictures other than one similar to typhoid fever.

The genus Salmonella comprises a group of gram-negative bacilli. They are midway between the typhoid and the coli groups in many of their characteristics. More than 150 distinct species have been described, and more are constantly being reported. Actually less than twenty are frequently found in human infections.

The organisms almost invariably invade the body by way of the gastro-intestinal tract, usually through contaminated food stuffs. They are rarely water borne. Thus, in speaking of Salmonella infections one thinks first of cases of endemic food poisoning with enteritis. The carrier state exists in many animals and humans. Most of these are asymptomatic. It is for this reason that public health measures directed at limiting the incidence of this disease are not very successful. There is no sex or age preference. However, there is a seasonal significance in that the disease is more common in the warm months.

The bacteria are divided into 6 groups labeled alphabetically A through F (table 1). The group A bacilli tend to resemble the typhoid bacillus while groups B and C come closer to the coli group. In group A the most important organism is S. paratyphi A. In group B the S. typhimurium is the chief one. It is a prominent cause of gastro-enteritis. In group C there are a number of important types, among which are 1) S. montevideo which was responsible for one of our cases, and 2) S. choleraesuis which caused the infection in our other case. Groups D and F contain organisms that are mostly responsible for animal infections, while group E has a few that infect both man and animals.

It is felt that any species of Salmonella capable of infecting men may produce any of the following clinical pictures:—

1) Continued fever of the typhoidal type.
2) Acute gastro-enteritis. This is the most common and is known as "food poisoning."
3) Localized infections with or without accompanying sepsis.
4) Asymptomatic infections or carrier states.

These four types may occur singly or in combination with each other. The blood cultures are frequently positive.

The pathogenesis of Salmonella infections apparently starts with the lymphoid tissue of Peyer's patches in the small bowel. Here the organisms multiply and gain access to the lymphatics, the lymph nodes, and ultimately the blood stream

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TABLE 1. *Abbreviated Kauffmann-White classification of commoner Salmonella*

Types	Somatic Antigens	Flagellar Antigens	
		Phase 1	Phase 2
Group A			
S. paratyphi A	(I), II, XII	a	—
Group B			
S. paratyphi B	(I), IV, (V) XII	b	1, 2
S. typhi-murium	(I), IV, (V)	i	1, 2, 3
S. derby	(I), IV	f, g	
Group C₁			
S. cholerae-suis (Kunzendorf type)	VI, VII		1, 5
S. montevideo	VI, VII	g, m, s	—
S. oranienburg	VI, VII	m, t	—
S. bareilly	VI, VII	y	—
Group C₂			
S. newport	VI, VIII	e, h	1, 2, 3
Group D			
S. typhi (E. typhosa)	IX (Vi) XII	d	—
S. enteritidis	(I), IX	g, m	—
S. panama	I, IX	l, v	1, 3, 4, 5
Group E			
S. give	III, X, XXVI	l, v	1, 7
S. anatum	III, X, XXVI	e, h	1, 6
S. senftenberg	I, III, XIX	g, s, t	—

* Eberthella typhosa may be classified serologically with the Salmonella, although it is not strictly a member of this genus.

by way of the thoracic duct. Localization in other organs such as the kidney, gallbladder, bone marrow, and the like is the result of hematogenous dissemination.

The typhoidal type is as its name implies. It is not of much concern urologically save that it may cause a picture of glomerulonephritis. One of the organisms which frequently produces this picture is the S. choleraesuis which was present in one of our cases. However, in our case it did not cause glomerulonephritis. It is interesting to comment here that in this case there were gastro-intestinal symptoms but the stool cultures were negative.

The second type of picture, acute gastro-enteritis, is, also, of not much concern urologically. One of the organisms frequently the cause of this picture is S. montevideo. This organism was the cause of the infection in our other case, but there were no accompanying gastro-intestinal symptoms. Yet the stools were positive on culture. Thus, you can see the frequent overlapping in the clinical picture.

Salmonella may cause localized infections anywhere in the body either with or without accompanying sepsis. Localized infections with all the commoner types have been reported but the strain most frequently responsible is S. choleraesuis which has pronounced invasive characteristics. One may get cholecystitis, endocarditis, meningitis, pneumonia, osteomyelitis, tonsilitis, salpingitis, otitis media, abscesses in various locations, and urinary tract infections.

TABLE 2 *Summary of bacteria causing pyelitis in 835 cases collected from literature by Mathe and Bell*

Bacillus coli	631	B proteus	8
Staphylococcus aureus and albus	89	B lactis aerogenes	7
Streptococcus	34	B typhosus	4
B acidi lactici	16	B pyocyaneus	3
Diplococcus	12	B paratyphosus	2
Miscellaneous	10	B enteritidis	1
Pneumococcus	8	B faecalis alcaligenes	1
B influenzae	8	Pseudodiphtheroid bacillus	1

TABLE 3 *Routine cultural studies of kidney urines, Pennsylvania Hospital*

Total number of specimens received (Feb 1933-Feb 1934)	466
Bacteriologically sterile (no growth in 48 hours)	357
Colon bacillus group	
B coli communior	7
B coli communis	17
B aerogenes	4
B acidi lactici	10
Paracolon bacillus	10
Bacilli of colon group (not separately identified)	12
Bacillus of paratyphoid group (not identified)	1
B faecalis alcaligenes	2
B proteus	4
B pyocyaneus	3
Friedlander's bacillus	6
Staphylococcus albus	20
Staphylococcus aureus	9
Nonhemolytic streptococcus	3
Micrococcus catarrhalis	1

As has been said, one may get a picture of nephritis but more usually the infections of the genito urinary tract are localized with no signs of infection elsewhere In a series of 835 cases of urinary infection, two were due to Salmonella (table 2) In another series of 466 cases there was one case caused by Salmonella organisms (table 3) Cystitis, pyelitis, pyelonephritis, and perinephritic abscess have been described A number of patients with renal calculi and Salmonella pyelonephritis have been reported, the most recent being by McLellan and Biezing in 1949 The diagnosis is difficult to make on clinical grounds because of the varied pattern of the disease The final proof rests on the bacteriological examination

CASE REPORTS

Below are described two cases of Salmonella infection whose admitting histories were directed entirely toward the urinary tract Both patients were seen at the Hines Veterans Hospital in 1951 They had pyuria and their urine cultures on repeated occasions showed Salmonella organisms Each patient had a different type and so could not have been a cross contamination

Case 1 A 49 year old white man, Ralph G H, felt well until about 2 days prior to admission in June 1951 (fig 1) At the time he had extreme frequency

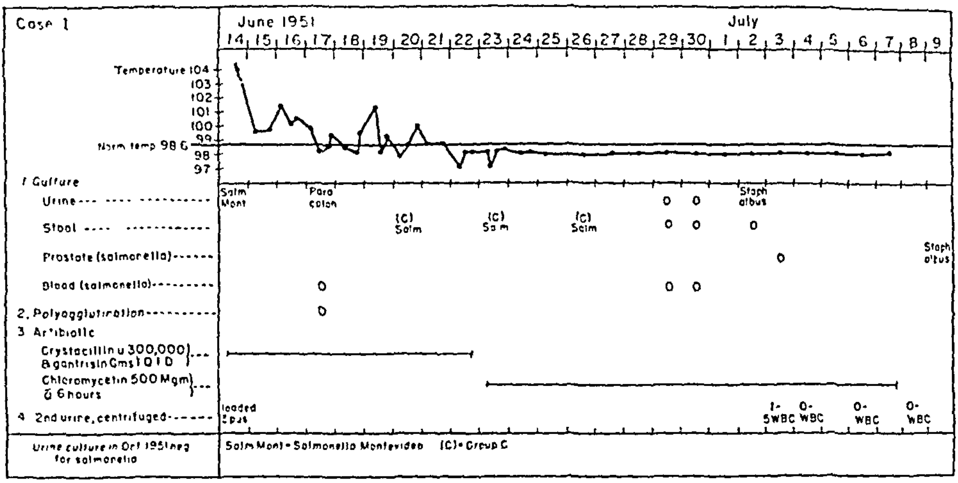

FIG. 1

of urination along with some dysuria. There was cloudiness of the urine, terminal hematuria, marked low back pain along with chills and fever. Prior to this he had had no genito-urinary symptoms. He denied ever having had gonorrhea or syphilis. A review of systems at the time of admission revealed no gastro-intentinal disturbance. His temperature was 103.6F. Accordingly he was admitted to the urological service. Physical examination was essentially negative except the genito-urinary tract. It might be mentioned that there was no abdominal tenderness. Both glass 1 and 2 urine specimens were cloudy, and it was unnecessary to centrifuge the specimen to see that microscopically the cloudiness was due to an increase in pus cells. The prostate was boggy and slightly enlarged. It was tender. The prostatic smear was loaded with pus cells. The white blood count was 14,500. A urine culture was taken and while it was growing the patient was started on penicillin and gantrisin. When the urine culture was reported as being of the Salmonella group, the medication was changed to chloromycetin. Stool cultures were taken and these, also, were positive for Salmonella. Blood cultures were negative, but it must be admitted that they were not taken until after he had been receiving medication. A Salmonella infection had not been expected at first. The specimen was sent to the Salmonella center where it was identified as S. montevideo. After treatment, three urine cultures and three stool cultures were negative before the patient was discharged. An excretory urogram was normal. At the time of discharge glass 1 and 2 urine specimens were both clear and the centrifuged sediment of the second glass showed only 2 to 3 pus cells per high power field. He was in the hospital 26 days. He returned for follow-up urine cultures. These were all negative when he was last seen and this was 3 months after being discharged.

Case 2. A 30 year old Negro, Earl H., was admitted in June 1951. The patient had had an intermittent right flank pain for 6 years. He stated that on occasions he had passed blood in his urine but on closer questioning one could not be sure of this, or whether it was just dark urine. There was no dysuria, diminution of the urinary stream, urgency, low back pain, or suprapubic pain. Occasionally the right flank pain would radiate into the right testicle. From

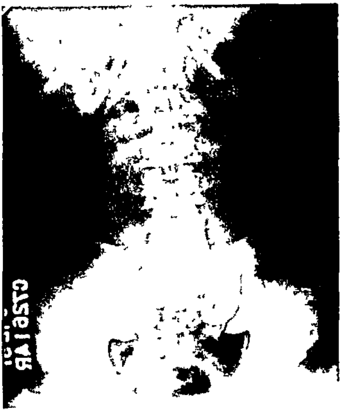

FIG 2

time to time he would have chills and fever. During the two weeks prior to entrance to the hospital he had had some nausea, vomiting, anorexia, and a "bad feeling in the upper abdomen." The patient had had gonorrhea previously; he denied ever having had syphilis. Physical examination was essentially negative except for the abdomen and the genito-urinary tract. He had marked right upper quadrant tenderness along with marked tenderness in the right costovertebral angle. The temperature was 101F. The urine was cloudy in glass 1 and 2. The centrifuged sediment of the second glass showed many pus cells and several red blood cells per high power field. An x-ray showed a calculus in the region of the right kidney (fig. 2). The prostate was enlarged, boggy, and somewhat tender. The prostatic smear had many clumps of pus cells (fig. 3). He was admitted to the urological service with a diagnosis of possible nephrolithiasis and chronic prostatitis. A urine culture was taken and while awaiting the report, the patient was started on penicillin and gantrisin. When the culture was reported Salmonella, the medication was changed to chloromycetin since

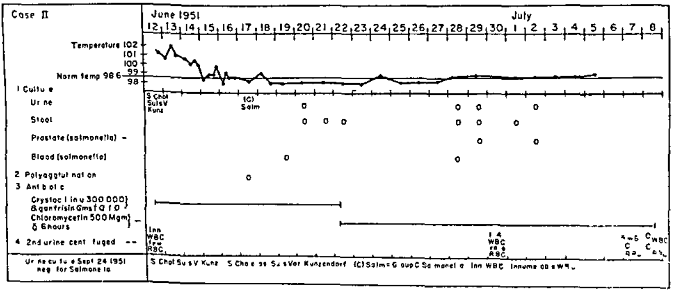

FIG. 3

that drug is supposed to be more specific for this infection. Excretory urograms, retrograde pyelograms, and gallbladder visualization films were taken. These showed the calculus to be anterior to the kidney. The diagnosis was made by the x-ray department, after a gastro-intestinal series, as being a coprolith of the appendix. The white blood count on admission was only 7,100. Blood and stool cultures were repeatedly negative for Salmonella organisms, but, it must be admitted, they were not taken until the patient had had some medication. The specimen was sent to the Salmonella center where it was identified as being S. choleraesius. Before being discharged from the hospital three urine cultures were obtained that showed no growth. A recheck of the urine before discharge showed glass 1 and 2 to be clear and the centrifuged sediment of the second glass to show 4 to 5 pus cells per high power field and no red blood cells. At the time of discharge he had no complaints. The patient was in the hospital 28 days. He was followed with periodic urine cultures for 2½ months with no evidence of recurrence.

As can be seen from the graphs both cases responded to penicillin and gantrisin as far as the temperature curve was concerned. However, in case 1 the stool cultures did not become negative until 7 days of chloromycetin therapy. Prostatic cultures of both were taken and they both showed no growth, but they were not taken until after therapy had been well started. Salmonella are stated to be most susceptible to chloromycetin and for this reason the patients were both switched over to that drug in order to reduce the possibility of the carrier state. This was before the large volume of work on the toxicity of chloromycetin had been reported. In a series of mild epidemics, sulfonamides have been shown to exercise some control. Penicillin works fairly well *in vitro* but it has not been very effective in clinical practice. In view of the toxicity of chloromycetin the probable next best choice of antibiotics would be streptomycin.

While it is true that the chronic urinary carrier is less common in Salmonella infections that it is in typhoid infection, still it is one of the important carrier states and it is to be desired that it be prevented. A chronic carrier may show recurrent systemic infection during periods when his immunologic response is poor.

These cases serve to emphasise that in patients with pyuria a urine culture is an essential in that not too uncommonly a rather rare organism of hematogenous origin may be the etiological agent. In such a case, if missed, the patient may get clinically well but remain a carrier if given inadequate treatment.

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EFFECTS OF RENAL PELVIC ANESTHESIA ON URINE FLOW IN DOGS

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With the development of a technique for the catheterization of ureters in conscious, unoperated dogs (Toth, 1950), it appeared feasible to anesthetize a part of the renal mechanism by infusing topical anesthetics into the renal pelvis and studying the effects of the anesthesia on volume output. The results of such an investigation are found in this report.

MATERIAL AND METHODS

Two trained female dogs, weighing about 14 kg. and in a 24 hour post-prandial state, were used. The animals had access to water prior to the experiments. The ureters were catheterized as reported previously (Toth, 1950), and urine rates were determined by counting the number of drops of urine issuing from the catheters every 2 minutes. With high urine flows the rate was determined for 2 minute periods by collecting the urine in small calibrated cylinders. In some experiments the animals were diuretic because of water administered by stomach tube shortly before the experiment. After a control urine rate was determined the anesthetic was infused into the renal pelvis from a 5 cc. syringe through the catheter under a pressure of 40 cm. H_2O. The solution was retained for 6 minutes under this pressure after which the syringe was removed and the excess solution was drained from the pelvis. The urine rate determination was then continued. One dog was anesthetized with pentobarbital sodium in several experiments. Although only one ureter was catheterized as a rule in each experiment, on three occasions both ureters were catheterized and urine rates determined separately from the two kidneys. In these cases the anesthetic was infused into one pelvis only. The topical anesthetics used were procaine hydrochloride and metycaine hydrochloride, varying in concentration from 2 to 8 per cent.

EXPERIMENTS AND RESULTS

A total of 20 experiments were performed on the 2 dogs, 15 experiments studying the effects of pelvic anesthesia and 5 controls in which water was infused into the renal pelvis. Figure 1 presents the data from a representative experiment on an unanesthetized dog. Although fluctuations in the urine output were present with this diuretic rate, pelvic anesthesia had no effect on volume output. The increase in volume during the first 2-minute period immediately after the pelvic infusion was probably due to incomplete drainage of the infused solution.

Figure 2 presents the data from an experiment on an anesthetized dog. The water diuresis was delayed by the pentobarbital sodium, a finding reported earlier (Toth, 1951), but the response to the pelvic infusion was again negative. Just as

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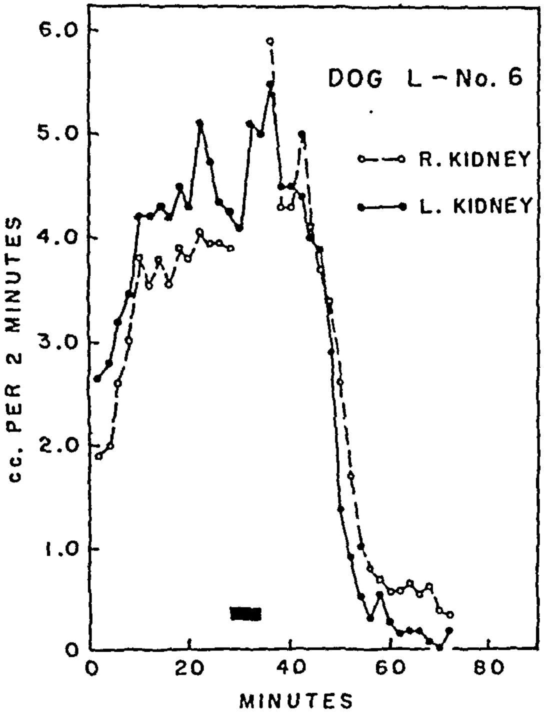

FIG. 1. Effects of renal pelvic anesthesia on urine flow. Dog without general anesthesia.

in figure 1 the curve shows an increased urine rate immediately after the pelvic infusion; but this again can be attributed to the incomplete drainage of the infused solution.

Table 1 summarizes the experiments performed on the 2 dogs. Dog L was conscious in all of the experiments but dog B was anesthetized in the majority of experiments because she was too restless. The experiments on dog L were from 47 to 80 minutes in duration and on dog B from 40 to 126 minutes.

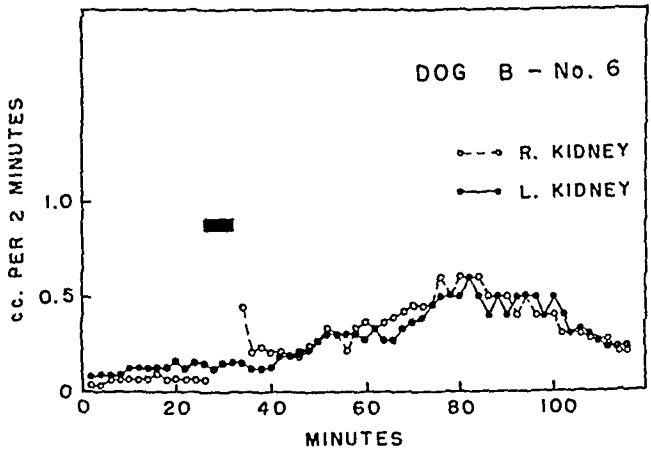

FIG. 2. Effects of renal pelvic anesthesia on urine flow. Solid blocks indicate periods during which 6 per cent procaine hydrochloride was infused into right renal pelvis. Dogs received 150 cc water by stomach tube 37 minutes before determination of urine rate began. Each point on curves is total urine output for kidney for preceding 2 minutes.

TABLE 1. *Summary of data on renal responses to pelvic anesthesia*

Dog	Exp No.	Exp. Procedure	Av. Control Urine Rate cc/2 min.‡	Exp. Response§ cc/2 min.
L	1	2% PrHCl in R. pelvis	.11	.20
	2	4% " " L. "	.10	.09
	3	4% " " R. "	.11	.08-.12
	4	4% " " " "	.10	.06-.05
	5†	4% " " " "	1.10	2.3-1.5-.61
	6†	6% " " " "	R: 3.83	R: 3.6-.57
			L: 4.42	L: 3.6-.91
	7†	8% MetyHCl in R. pelvis	2.03	2.87
	8	8% " " " "	R: .05	R: .05-.06
			L: .05	L: .02-.02
	9	Water in L. pelvis	.13	20
	10	" " " "	.37	.21-.11
	11†	" " R. "	.38	2.15-1.14
B	1	2% PrHCl in R. pelvis	.16	.16
	2	4% " " " "	.12	.10
	3*†	4% " " L. "	.07	.05-.08
	4*†	6% " " " "	.11	.08-.17
	5†	6% " " " "	.63	1.49-1.74-1.77-.88
	6*†	6% " " R. "	R: .06	R: .25-.36-.53-.34
			L: .13	L: .18-.31-.50-.37
	7*	8% MetyHCl in R. pelvis	.05	.45-.29
	8*	Water in R. pelvis	.09	.16-.07
	9*†	" " L. "	.08	.12-.23-.38

PrHCl—Procaine hydrochloride.
MetyHCl—Metycaine hydrochloride.
* Dog anesthetized with pentobarbital sodium prior to catheterization.
† Dog received approximately 150 cc H_2O per os before expt.
‡ Average rate for 20 minutes just preceding pelvic anesthesia.
§ The first figure is average rate for first 20 minutes after renal pelvic anesthesia: additional figures are similar values for subsequent 20-minute periods.
R: Right kidney; L: Left kidney.

DISCUSSION

For a topical anesthetic to be effective the solution must have a threshold concentration. The concentration of a solution infused into the renal pelvis will be reduced because of dilution by the urine already present in the pelvis. The extent of the dilution depends on the volume of urine present, and this in turn on the volume of the pelvis. Bojesen (1949) reported pelvic volumes of 4.3 cc during diuresis in dogs weighing 20–23 kg. and that the pelvic volume varied directly with the rate of urine formation. It is safe to assume that in the smaller dogs used in the present work, and with a smaller diuresis, the pelvic volume was not as large. The concentrations of procaine infused in the first experiments were 2 and 4 per cent, the ones usually employed clinically. Stronger solutions were used in the later experiments to offset the dilution factor and thereby maintain an effective concentration.

The pelvic infusion pressure must be of such magnitude as to overcome the renal pressure already present if the solution is to get up into the pelvis. A 40 cm. water pressure was used for the pelvic infusions, a pressure high enough to force the solution into the pelvis even with the maximum diuresis occurring in these experiments. Morales and co-workers (1952) reported pelvic pressures no higher than 30 cm. water although the diuresis in their dogs reached a value of 9 cc per minute for the two kidneys.

High infusion pressures into the renal pelvis could result in escape of the solution down the ureter on the outside of the catheter and thereby not remain in the pelvis to produce anesthesia. That no such leakage took place was proved by infusing a dilute indigo carmine solution under 40 cm. water pressure into the catheter and observing the ureteral orifice through a cystoscope in the bladder.

For a topical anesthetic to affect urine flow it is reasonable to assume that it must get to a vital part of the renal unit, particularly to some part of the tubular mechanism. From an extensive review of the literature on retrograde pyelography, and from his own work, Narath (1951) concludes that the contrast medium used in pyelography succeeds in entering the collecting tubules of one or a few neighboring reniculi, and that sometime all reniculi may be involved. The failure of the anesthetic solutions infused into the renal pelvis to affect volume output of a kidney probably means that anesthesia of the pelvis and collecting tubules does not affect urine output. Judging from Narath's observations, it is unlikely that the anesthetic solution passed as high as the distal or proximal tubules. Therefore the effects of anesthetizing these structures remains unanswered.

Local anesthesia of one renal pelvis and/or the pressure in the pelvis produced by anesthetic solutions or water alone resulted in no reflex change in urine output in the contralateral kidney. The two curves in each of figure 1 and 2 show a surprising uniformity of response, especially with low urine rates.

SUMMARY

Infusions of topical anesthetic drugs into the renal pelvis of conscious and anesthetized dogs are without effect on urine rates in the ipsilateral and contralateral kidneys in dogs with normal and water diuretic urine outputs.

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VENOUS POOLED NEPHROGRAMS: TECHNIQUE AND RESULTS

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Since the development of nontoxic iodides for excretory urography, several techniques have been developed for increasing the intensity of the renal shadow. The most universally successful method has been that of translumbar aortography, but it is impractical for a routine procedure. Several assistants are necessary, a large and potentially dangerous needle is used and the patient must be heavily premedicated or given general anesthesia in order to carry out this procedure.

Authors[1, 2, 3] have developed techniques of obtaining "nephrograms" in which the essential feature of the technique is that of rapid injection of a nontoxic iodide over a period of one to five seconds, followed by properly timed roentgen exposures of the kidney areas. The feature common to these techniques is that a large needle of twelve to fifteen gauge is utilized and a large vein is cannulated. Failures in the technique have been attributed to extravasation of the injected medium and to difficulties in inserting large needles into patients who have relatively small veins. It is the purpose of the authors to introduce a method of obtaining nephrograms which has been satisfactory in our hands, and is sufficiently simple to be particularly applicable to patients with small veins. No special equipment is required and the use of local anesthesia is regarded as unnecessary.

Equipment consists of 25 cc of 70 per cent urokon, 25 cc syringe, a No. 19-21 gauge needle and a tourniquet. The patient is centered on the x-ray table so that the kidney areas are directly over the center of the film. A vein in the dorsum of the wrist or hand is selected for injection and one drop of urokon is injected to test the patient for sensitivity. After a waiting period of 2–3 minutes the arm is raised allowing the peripheral veins to empty and the tourniquet is applied high on the arm, tightly enough to produce venous occlusion. The urokon is injected slowly over a period of 15 to 30 seconds. This pools the medium in the veins of the lower arm. At the end of the injection the tourniquet is loosened with the needle and syringe in place. Simultaneously, the patient's arm is raised and after a moment the needle and syringe are withdrawn. The latter maneuver prevents hematoma formation. At the end of fifteen seconds a roentgen exposure is obtained. Another roentgen exposure is taken one minute after the termination of the injection (45 seconds after the first roentgen exposure). These films have been taken with the patient holding his breath in expiration.

Accepted for publication October 22, 1953.

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TABLE 1. *Results of 55 nephrograms*

	No.	Per cent
Excellent	24	45
Good	19	35
Fair	4	7
Poor	8	14
Unprepared Patients (20)		
Excellent	7	35
Good	6	30
Fair	4	20
Poor	3	15
Prepared Patients (35)		
Excellent	17	48
Good	13	38
Fair	0	0
Poor	5	14

TABLE 2. *Results of nephrograms obtained at varying times after release of tourniquet*

	Excellent	Good	Fair	Poor
10 seconds (9)	3	2	2	2
15 seconds (41)	19 (46%)	14 (35%)	3 (7%)	5 (12%)
17 seconds (1)	1			
22 seconds (2)		1		1
60 seconds (23)	6 (25%)	7 (29%)	4 (18%)	6 (25%)

TABLE 3. *Reactions to 70 per cent urokon with 63 nephrograms*

	No.	Per cent
Local		
No pain	19	31
Slight pain	32	51
Moderate pain	6	9
Severe pain	4	6
Not stated	2	3
Systemic		
No reaction	45	71
Nausea	10*	16
Vomited	7	11
Slight urticaria	1	1.6

* One patient had syncope for five seconds.

A vein on the dorsum of the wrist or hand is recommended, but in several cases this has not been practical and the antecubital vein has been utilized with no noticeable difficulty other than perhaps a slightly increased amount of pain from distending the arm veins contrary to the flow of blood in the arm.

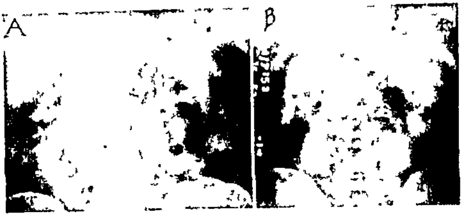

FIG. 1. Normal nephrogram. *A*, preliminary film. *B*, nephrogram obtained 15 seconds after release of tourniquet.

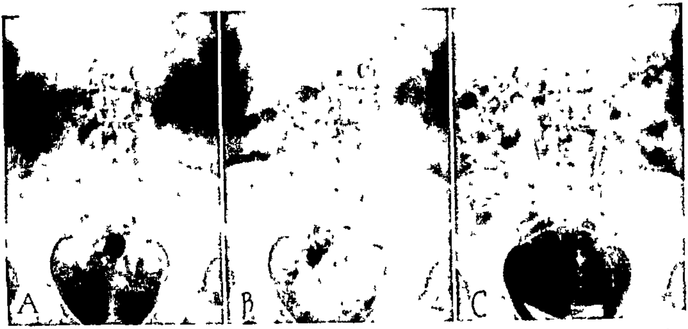

FIG. 2. Normal nephrogram of patient with left double kidney. *A*, preliminary film. *B*, nephrogram obtained 15 seconds after release of tourniquet. *C*, 15 minute excretory film. Patient had no preliminary preparation.

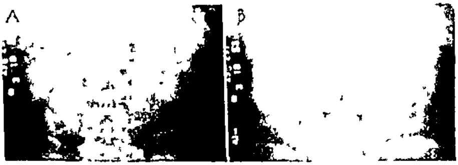

FIG. 3 Normal nephrogram. *A*, preliminary film. *B*, nephrogram obtained 15 seconds after release of tourniquet. Note left adrenal. Patient had no preliminary preparation.

A total of sixty-three pooled nephrograms was obtained in 59 cases. Eight of these nephrograms were discarded because of technical errors; e.g., roentgen exposures were made and the films were developed and processed by student x-ray technicians and an appreciable percentage of error was to be expected. Of the fifty-five nephrograms available for study, thirty-five were performed on patients who had been prepared for excretory urograms, and twenty were performed on patients who had arrived in an unprepared state. These results are tabulated in tables 1 and 2 and show that 80 per cent of the nephrograms were satisfactory. In the prepared patients, 86 per cent of the nephrograms were satisfactory, a percentage not at variance with nephrograms by rapid injection techniques. During the development of this series, exposures were made at varying times, and it was the authors' impression that an exposure 15 seconds after the release of the tourniquet gave the most satisfactory group of x-rays.

COMPLICATIONS

The immediate complications are tabulated in table 3. Approximately one-third of the patients had no pain upon injection and the remainder of the patients observed that the pain disappeared as soon as the tourniquet was released. Two patients had pain which persisted for five minutes after the release of the tourniquet.

No nephrogram had to be discontinued because of extravasation of the dye. In 2 cases, at the beginning of the injection, it was apparent that some of it was leaking out of the vein, so the procedure was momentarily discontinued and started again in the opposite arm.

Late complication: One patient returned 1 week after his nephrogram with a complaint of a small, tender nodule in his antecubital fossa. At the site of injection the patient had a local thrombus approximately two centimeters in length. This was the most severe complication observed in this series.

DISCUSSION

It has been our experience that pooled arm nephrograms provide a simple method of defining the renal shadows, thereby helping to distinguish the kidneys from other upper abdominal masses. Although this series is not large enough to demonstrate the full range of problems in which nephrograms may prove valuable, the study of our cases and those of others who have utilized the rapid injection technique indicate that nephrograms are a distinct aid in defining the area of functioning renal parenchyma. We have not observed the "arterial phase" when using the pooled arm technique, probably because of an appreciable dilution of the dye in the arm veins. Absence of this phase however seems to have little bearing on the quality of nephrograms as the percentage of satisfactory nephrograms by the authors' technique compares favorably with those using the rapid injection method.

This method has a further value of considerable practical importance in that it provides a satisfactory method of study of the upper urinary tract in unprepared patients. To send patients home and require that they undergo preparation and return on a second visit for excretory urography has always been an inconvenience. The nephrogram and 4 minute excretory film using the more concentrated dye has effected a great saving in time and money for the patient. See figures 1, 2 and 3.

SUMMARY

A simplified technique for obtaining nephrograms is presented. This consists of pooling of the radio-opaque medium in the veins of the arm, followed by roentgen exposures fifteen and sixty seconds after the release of the medium. The results of fifty-five nephrograms with prepared and unprepared patients are tabulated and illustrative cases are shown.

We are indebted to the Mallinckrodt Chemical Works and Dr. Melvin Thorpe for the supply of urokon which was used in this series.

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VASO-EPIDIDYMOGRAPHY AND VASOSEMINAL VESICULOGRAPHY

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The history of radiography of the male genital tract does not reveal the same degree of enthusiasm or thoroughness that has characterized radiographic investigation of the rest of the genito-urinary tract. It was not until 1951 that the lower portion of the genital tract, i.e., the terminal portion of the vas and the epididymis, was studied radiographically.

The first attempt to probe the genital passages was carried out successfully in 1895 by Klotz and Wassefield. They catheterized the ejaculatory ducts with special sounds by means of direct urethroscopy. About the same time similar work was also carried out by Luys in France.

It was not until McCarthy and Von Lichtenberg (1906) perfected the irrigating urethroscope that examination and instrumentation of the posterior urethra became relatively safe. In 1913 Belfield performed the first roentgenography of the seminal vesicles by means of injecting collargol through the scrotally exposed vas deferens. Belfield's work was soon followed by Young and Waters and other workers. In 1939 Wilhelm was able to obtain 121 vesiculograms in 127 attempts by means of vesiculography through the vasoseminal route. Pereira, in South America, has been one of the most ardent proponents of radiographic study of the genital tract. His excellent articles dealing with the roentgenographic interpretation of seminal vesiculograms should be read by those interested in this subject.

Vaso epididymography was introduced in 1951 by a group of French workers—J. Boreau, P. Hermann, B. Vassel, and F. Tua. They exposed the vas in the upper part of the scrotum, whereas Loizzi, in Italy, exposed the vas in the inguinal region. Tucker, Yanagihara, and Pryde have recently reported in the American literature on this subject. Their technique differs from ours in that they used thorium and "thorotrast" as contrast media.

PURPOSE

The French and Italian workers have emphasized the importance of this work in the study of pathologic lesions of the male genital tract and in the study of infertility in the male. As is the case with all new radiographic techniques, its value or clinical application can not be definitely established until sufficient information has been gathered to determine its usefulness. It remains for the urologic profession to determine the advantages and disadvantages of this technique in the study of the male genital tract, particularly in the diagnosis of lesions of the male genital tract and in cases of male sterility.

It was apparent to us from the very beginning of our work that the study of sterility problems in the male could be greatly aided and facilitated by vaso-epididymography and that seminal vesiculography was of inestimable value in certain selected cases as will be demonstrated. We are convinced that the routine employment of epididymography for diagnostic purposes is unnecessary but that

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Read at annual meeting, Mid Atlantic Section, American Urological Association, Washington, D.C. April 22, 1954.

the procedure is feasible and desirable in the diagnosis and treatment of certain specific diseases or lesions of the lower vas and epididymis.

In the past 6 months we have performed vaso-epididymography and seminal vesiculography on 20 patients and in this paper will present 9 cases demonstrating different pathologic lesions found in the lower genital tract of the male.

TECHNIQUE

Under local anesthesia (1 per cent xylocaine solution), a 2 cm. portion of vas is exposed through the upper portion of the scrotum. While the vas is steadied by two pieces of suture material, a No. 26 hypodermic needle is inserted into its lumen and 1 cc of 70 per cent urokon is injected toward the epididymis. The needle is then removed and re-inserted into the lumen of the vas in the opposite direction and 1.5 cc of 70 per cent urokon is injected. The needle is then removed, the vas is replaced into the scrotum, and the scrotal incision closed. Exposure and injection of the opposite vas are performed at the same time and in the same manner.

A plain film of the bladder region is then taken for the purpose of viewing the seminal vesicles using the same radiographic technique recommended for cystograms.

The patient is then turned on his abdomen and a small cardboard plate of Eastman non-screen film is inserted beneath the scrotum. The tube is kept at a distance of 36 inches and is angled from 15 to 20 degrees. The exposure is taken at ¼ second using 100 MA and from 50 to 65 KV, depending on the size of the scrotum. A scout film may be taken beforehand to determine the intensity of the exposure.

A second epididymogram is taken after the epididymis has been gently massaged and the testicle rotated to another position. The patient is then allowed to void and another anteroposterior plain film is taken of the bladder area for the purpose of viewing the seminal vesicles without dye in the bladder.

We have succeeded in obtaining excellent vasograms, epididymograms, and seminal vesiculograms in more than 95 per cent of the cases by utilizing this technique

ANATOMY

For purposes of aiding in the interpretation of the vaso-epididymograms, a brief review of the anatomy of the vas is presented. The vas is 40 to 45 cm. in length, and begins at the globus minor of the epididymis where it forms an acute angle known as vaso-epididymal kink. The ascending portion of vas begins with numerous convolutions for a distance of from 2 to 4 cm. after which it straightens out and becomes a narrow tube from 2 to 3 mm. thick with a lumen of .16 mm. It then courses along with the structures of the spermatic cord through the inguinal canal. The descending portion of the vas develops just beyond the internal inguinal ring as the vas dips downward and medially to cross in front of the lower portion of the ureter. Reaching the medial side of the seminal vesicle, the vas passes downward and medially in contact with the seminal vesicle as it gradually approaches the opposite vas. In this area, the vas lies between the fundus (floor)

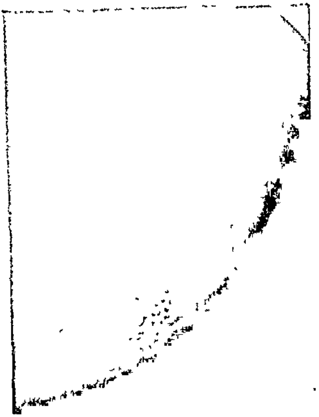

FIG. 1. Normal epididymogram (A-P view)

of the bladder and the rectum and is invested together with the seminal vesicle in a sheath derived from the retrovesical portion of subserous fascia. At the fundus of the bladder, about 4 cm. above the prostate, it becomes enlarged and tortuous and forms the ampulla of the vas. At the base of the prostate, the vas becomes greatly narrowed and is joined at an acute angle by the duct of the seminal vesicle to form the ejaculatory duct which traverses the prostate behind its middle lobe and opens into the prostatic urethra, close to or within the orifice of the prostatic utricle.

CASE STUDIES

Epididymograms and seminal vesiculograms were done on twenty patients The following conditions will be demonstrated: 1) normal vaso-epididymogram; 2) acute epididymitis, nonspecific; 3) chronic epididymitis, nonspecific; 4) post traumatic epididymitis; 5) tuberculous epididymitis; 6) adenomatoid tumor of the epididymis; 7) bilateral testicular tumor; 8) sterility problem; 9) carcinoma of the prostate; 10) ectopic ureter opening into the seminal vesicle.

As this paper is being presented primarily for a report on vaso-epididymography, only the unusual seminal vesiculograms will be demonstrated.

Figure 1 represents a normal epididymogram. The vas courses downward from the point of injection becoming convoluted at the end. The globus minor begins at the vaso-epididymal kink. The contrast medium becomes feathery in appearance at this point. The body of the epididymis is forked which is one of the normal variations according to the French workers. The dye stops at the globus major.

In one of our cases the diagnosis was acute, nonspecific epididymitis. An epididymogram was done because of academic interest. In this film (fig. 2) the contrast medium shows a "pooling" within the epididymis. Whether this represents abscess formation or just extreme dilation of the tubules in uncertain.

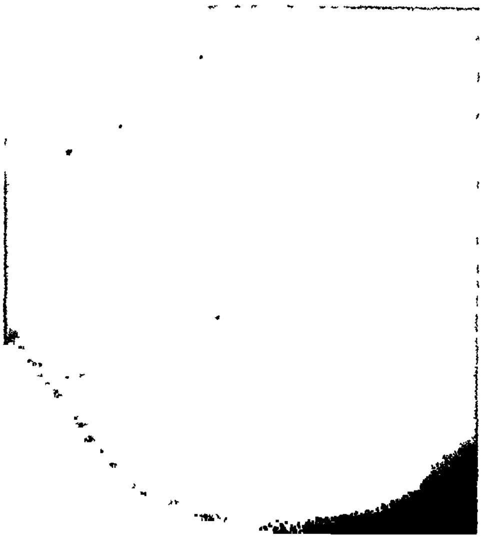

FIG. 2. Acute left epididymitis. Normal right epididymis (A-P view)

FIG. 3. Chronic epididymitis (A-P view)

A 72 year old white man had a past history of repeated episodes of chronic recurrent bilateral epididymitis. At this time he had no symptoms referable to his epididymis. On examination, the globus major on each side was indurated and enlarged but not tender. The patient was in the process of being worked up for persistent pyuria which had not responded to different antibiotics during the previous 1½ year period of intermittent treatment.

The epididymogram reveals bilateral pooling of dye (fig. 3) The vasa are normal. Following bilateral vasectomy the pyuria disappeared for reasons not clearly established. It is possible that the injection of the dye helped to eradicate the chronic infection in both epididymides which was the source of the chronic urinary infection.

Epididymograms were carried out routinely in patients having benign prostatic hypertrophy inasmuch as these cases were subjected to bilateral vasectomy

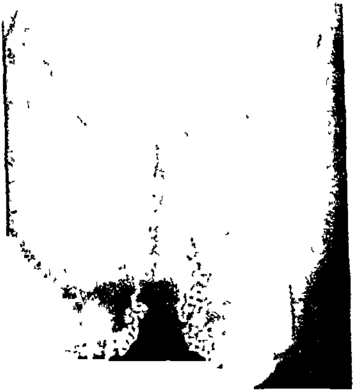

FIG. 4. Post traumatic right epididymitis. Normal left epididymis (P-A view)

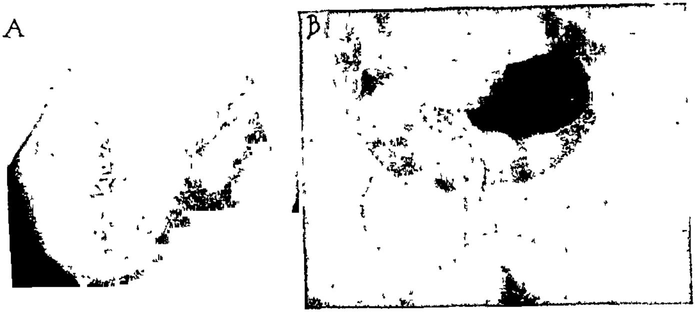

FIG. 5. *A*, tuberculous epididymitis. Vasoscrotal fistula (P-A view). *B*, tuberculous seminal vesiculitis on right. Left seminal vesicle absent.

prior to surgery. In one of our cases a pooling of dye was noted on the left while the right appears normal (fig. 4). The patient had no past history of epididymitis but at the age of 14 experienced an injury to the left testicle with "swelling" of that organ. Although the patient experienced no further difficulty with the testicle the x-ray reveals that permanent damage of the epididymis had taken place.

A 78 year old man had known pulmonary tuberculosis along with chronic epididymitis which was presumably of tuberculous origin. He had been admitted to the hospital for an epididymectomy, as the epididymis was large, indurated, and slightly tender with a draining sinus or fistula on the right side of the scrotum.

The vasogram on the right reveals a vasoscrotal fistula with no dye passing into the right epididymis (fig. 5, *A*). The seminal vesiculogram on the right re-

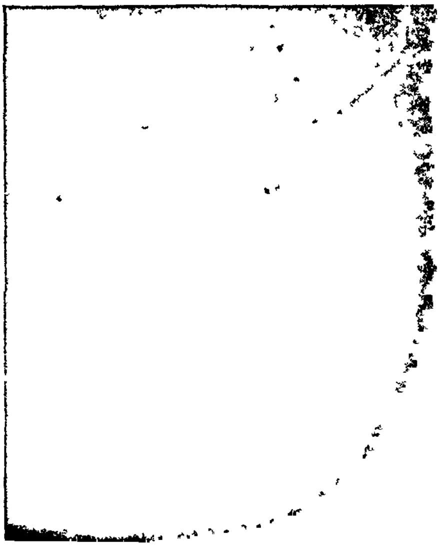

FIG. 6. Adenomatoid tumor of globus major of epididymis (P-A view)

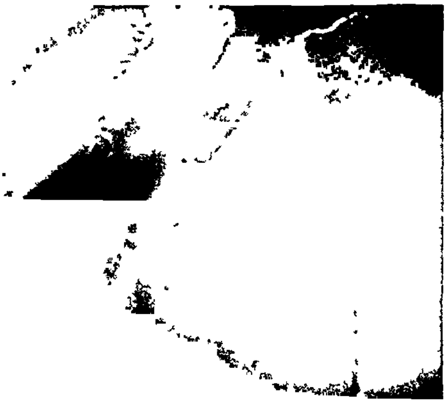

FIG. 7. Bilateral testicular tumor. (Film taken in operating room with portable x-ray unit)

veals a contracted lumen which is evidence of chronic inflammation (fig. 5, *B*). A left seminal vesiculectomy had been done 25 years previously which explains blockage in upper left vas deferens.

A 23 year old Negro was admitted to the hospital because of "testicular" mass. On examination the globus major of the right epididymis was large, rounded, firm, and nontender. The testicle itself was normal.

The epididymogram reveals the globus minor to be normal (fig. 6). The body of the epididymis is seen to widen as the globus major is approached, and no dye is seen in the latter.

The operative specimen proved the mass to be an adenomatoid tumor of the globus major of the epididymis.

A 60 year old white man was admitted to the hospital because of masses in

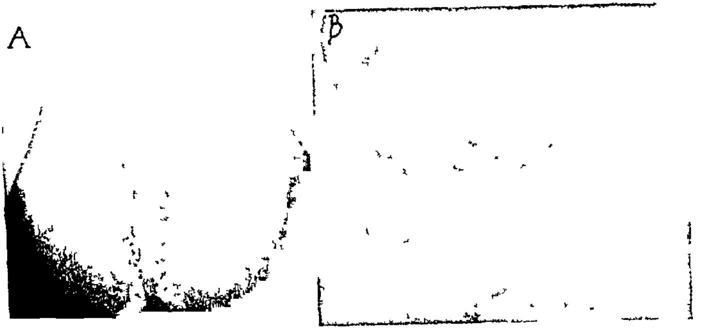

Fig 8 *A*, sterility study Note block in region of globus minor (P A view) *B*, sterility study (normal seminal vesicles)

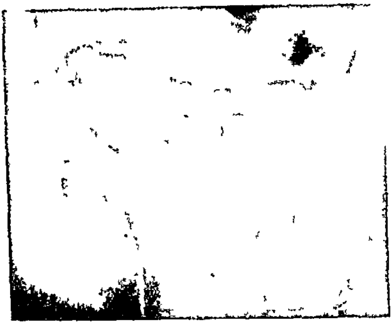

Fig. 9 Carcinoma of prostate with involvement of seminal vesicles

each testicle. The epididymogram was taken in the operating room prior to bilateral orchiectomy, which was carried out for bilateral seminoma.

The vas appears normal bilaterally (fig. 7). The right epididymis fills well, the dye being spread out a little wider than usual. The left epididymis is crescent shaped which is most likely due to extrinsic pressure.

A 31 year old white man had been married 9 years and was unable to impregnate his wife. Examination revealed the patient to be aspermic. The testicles were normal in size and consistency. A vaso-epididymogram and seminal vesiculogram (fig. 8) were carried out to determine the presence or absence of a blockage within the seminal tract The patency of the vas from the globus minor to the posterior urethra bilaterally was established. Blockage within the ductus epididymis was demonstrated, a testicular biopsy was done subsequently which revealed normal spermatogenesis. It was our opinion that this patient represents a good candidate for vaso-epididymostomy.

For the sake of completeness and to illustrate the value of vasography in conjunction with seminal vesiculography, the following cases will be presented.

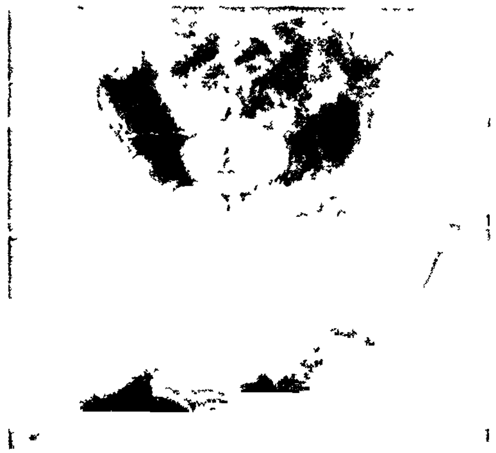

FIG. 10. Ectopic ureteral opening into right seminal vesicle. Eight minute film using approximately 15 cc 70 per cent sodium urokon. Note dilated ureter adjoining seminal vesicle.

A 53 year old white man was admitted to the hospital because of difficult urination. He had a transurethral resection and bilateral partial vasectomy some years previously for carcinoma of the prostate. On rectal examination, it was found that the prostatic tumor had extended laterally into the perirectal tissues and superiorly into the seminal vesicles. A seminal vesiculogram was done to determine the extent of the involvement of the vesicles. As can be seen on the film (fig. 9), the right vesicle and the medial portion of the left vesicle show a markedly narrowed lumen which represents encroachment into the seminal vesicles by the invading tumor.

This case will be presented in greater detail in a separate paper by Dr. Albert E. Goldstein and one of the authors (E. H.). Suffice it to say that this represents the tenth reported case of an ectopic ureter opening into a seminal vesicle correctly diagnosed prior to surgery.

The films shown here (fig. 10) were taken by the method described. It was necessary to use approximately 10 cc of 70 per cent urokon to demonstrate the ectopic ureter.

SUMMARY

The most impressive series of epididymograms has been gathered by Boreau, Ellsini, Hermann, Vassel and Fua. They have found that the procedure is harmless. The mucosa of the vas is not altered by the injection of dye, and the patency of the vas is not disturbed by the procedure. The last statement has been corroborated by Pereira.

In several instances we have removed, in connection with prostatectomy, vasa previously injected, and have found them in every respect undamaged. In one case we performed bilateral injection preliminary to bilateral epididymovasostomy and, after the operation, found numerous spermatozoa present in the semen. We believe therefore that vas puncture followed by the injection of urokon 70 per cent is innocuous.

We wish to emphasize again that it is unnecessary to use this procedure in the diagnosis of acute or chronic epididymitis and other pathological lesions which have heretofore caused the urologist little difficulty. We have employed this radiographic procedure in such cases in order that we might determine the roentgenographic lesions produced in the male genital tract by the various pathologic conditions and obstructive lesions.

We concur with the French and South American investigators that this new radiographic technique will lend itself admirably to the study of sterility in the male. This procedure enables one to study, graphically, the seminal tract from the testicles to the posterior urethra. It is an invaluable aid in determining whether or not vaso epididymostomy is feasible, providing testicular biopsy and/or aspiration of the globus major of the epididymis reveals active spermatogenesis.

It is, of course, necessary to carry out further investigative work along these lines to ascertain the true value of this procedure. In a subsequent article we plan to present a study of sterility in the male indicating the value of vaso-epididymography in determining the presence and location of obstruction within the seminal tract.

Vaso epididymography combined with vasoseminal vesiculography is a valuable radiographic procedure in the diagnosis of congenital anomalies of seminal vesicles, ejaculatory ducts, vas deferens and epididymis.

We wish to extend our gratitude to Dr. Antonio T. Tiongson, assistant resident in Urology, for his assistance in this study.

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A NEW STONE BASKET

BENJAMIN LEVANT

From the Department of Urology, Montefiore Hospital, Pittsburgh, Pa.

The transurethral approach to removal of ureteral calculi has great appeal both to patient and urologist. The procedure is recommended for stone in the lower ureter. To one who has had moderate success in dealing with ureteral calculi this way, there is no denying the feeling of success amounting almost to smugness as he extracts it from the ureter, into the bladder, and especially when he delivers it to the patient. Unquestionably, the patient is grateful if he can avoid a surgical procedure, or avoid repeated attacks of colic until he passes the calculus.

For many years different types of stone extractors have been used and discarded because of the amount of injury to the ureter and patient; the complications were worse than the original illness. What started out to be a conservative procedure turned into a prolonged septic illness with emergency surgery in many cases. Those of us who have used stone baskets know of the amount of damage done to the ureter as one visualizes the basket as it is withdrawn into the bladder. Many reports have been made of broken basket-wires getting caught in the ureter, even broken shafts, necessitating immediate surgery for their removal. The result of these experiences, not necessarily your own, is that you approach transurethral ureterolithotomy with timidity and apprehension. In fact, many urologists prefer surgical ureterolithotomy to this procedure.

I therefore proposed 4 years ago the idea of making a stone basket without metal or breakable parts, retaining in the main, the design of the Johnson basket. I proposed nylon strands on a ureteral bougie using 3 strands instead of 4, so as to allow more room to trap the stone. After 3 years of experimenting, we have a model which I have found satisfactory and safe (fig. 1). The nylon stranding which makes up the basket runs down the full length of the shaft making it exceedingly strong. In addition to having 3 strands of solid nylon, you also have the woven nylon covering, adding doubly to the strength of the instrument. The nylon in the filiform end is actually a continuation of the nylon in the basket; thus, to all intents and purposes, the instrument is in one piece. Another advantage lies in the fact that nylon will take a great deal more bending and flexing than metal and, as a result, the possibility of breakage is practically nil. The shaft is a graduated 8F ureteral bougie, opaque below the basket, with opaque filiform above. It can be used with the Brown-Buerger cystoscope or McCarthy panendoscope with equal ease.

The diagnosis of ureteral calculus is usually established by excretory urography; this can be confirmed by retrograde study, if necessary. The patient should be anesthetized preferably by low spinal or pentothal intravenously before cystoscopy. The basket is then passed through the cystoscope and up the ureter

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Read at annual meeting, Northeastern Section of the American Urological Association, Shawnee-on-Delaware, Pa., September 15–18, 1953.

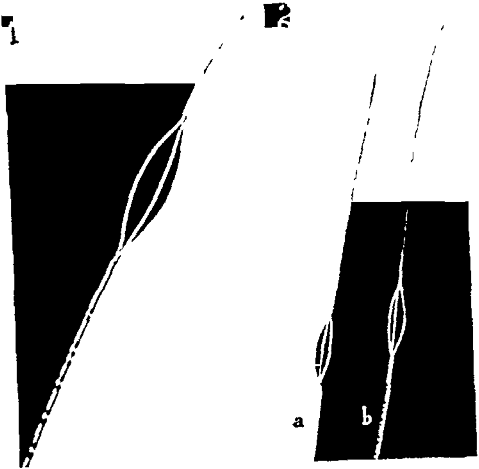

Fig. 1

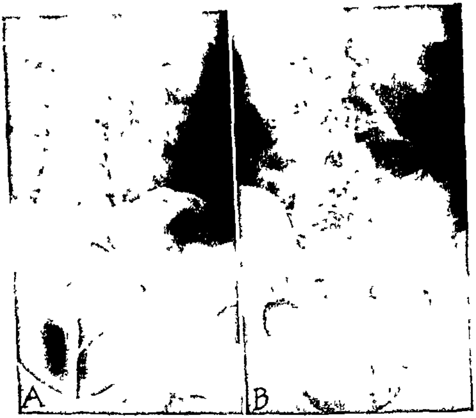

Fig 2

just beyond the calculus. See figure 2. Then pull it out slowly without twisting it, as twisting closes the lumen of the basket. If unsuccessful at first, the basket can easily be re-inserted several times with safety.

With this basket you will notice a minimum of trauma as you withdraw it into the bladder. You will notice also that once the basket passes the calculus, the lumen is completely open in the ureter because of the strength and flexibility of the nylon strands After removal of the basket with or without the stone, it is wise to pass a ureteral catheter to the kidney pelvis and leave it indwelling for 1 or 2 days. After all, a certain amount of spasm or edema may result from any instrumentation. The indwelling catheter will prevent unnecessary suffering caused by tissue reaction. Thus the entire procedure will remain a satisfactory conservative experience to the patient and urologist.

The basket is made with the regular 1 inch filiform or the 6 inch filiform with straight or spiral tip. The longer filiform is designed to enable the operator to more easily re-insert the basket if necessary, as he can visualize the basket in the bladder while a portion of the filiform is still in the ureter.

I wish to acknowledge my gratitude to C. R. Bard, Inc. for co-operation in making this basket.

412 Jenkins Arcade Bldg., Pittsburgh, Pa.

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PROSTATECTOMY UTILITY FORCEPS: A NEW INSTRUMENT

ALLAN K SWERSIE

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For several months, in my operative bladder work, I have been using to good advantage an instrument which on the basis of its functional value may be considered a prostatectomy utility forceps

As indicated in figure 1, the instrument in shape is a modification of the common sponge stick with angulation of the handle, which greatly facilitates control The blades have oval openings with moderately coarse serrations on the inner surface The width of the blades conform appropriately for use in deep recesses of the bladder and prostatic fossa The shank is 10 inches long, adequate to attain access to deep operative zones in patients with pendulous abdominal walls

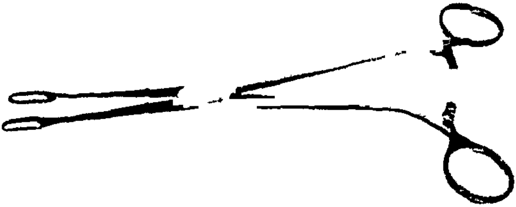

FIG 1

The forceps is adaptable for many purposes, the most common of which I have found to be the following —Removal of clots and calculi, traction on the prostate, spreading the prostatic fossa for inspection, grasping adenomatous remnants, insertion and removal of packing, and picking up ragged mucous membrane edges or internal orifice flaps

Its ready availability close to the operator will prove to be a time saver in dispensing with the search for tools of single purpose in disarranged instrument trays

The manufacturer of this instrument is the KNY-Scheerer Corporation, 35 East 17th St , New York, N Y

123 E 83rd St , New York 28, N Y

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AN IRRIGATING SYSTEM FOR TRANSURETHRAL SURGERY

MILTON B. OZAR

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A simple method for the sterile transportation of irrigating fluid for transurethral resections to a water tower was devised at the University of Kansas Medical Center. The disadvantages of frequent hoisting of a 5 gallon water bottle to the top of a tower, maintaining sterility in the process, are apparent It was felt that a system utilizing sterilizable units such as 5 gallon bottles was preferable to the construction of a large permanent tank. In addition, we felt that a nonhemolytic irrigating fluid should be used and 5 gallon units of 1.1 per cent glycine are easily prepared.[1] The 1.1 per cent glycine is prepared by adding 2000 cc of autoclaved 11 per cent glycine to each 5 gallons of sterile water. The system shown herein is practical, inexpensive and simple to operate.

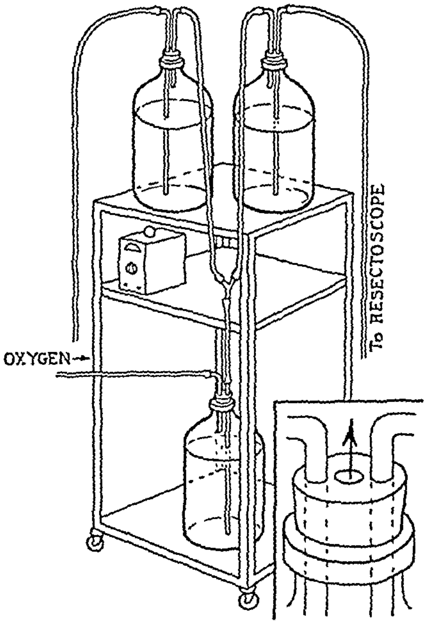

FIG. 1

The method employs a pressure system to force the irrigating fluid from a ground-level bottle to a bottle, or bottles placed on a tower. The pressure source utilized in our system is derived from an oxygen outlet installed in the operating room. A tank of oxygen could just as well be used. Only a minimal flow of oxygen for 5 minutes is necessary, ranging from 3–4 L/min. (50 pounds pressure) to force the fluid from ground level to the elevated bottles.

A 3-holed stopper is used on the elevated bottles. One of the openings allows the escape of air from the uppermost bottles, so that no pressure is accumulated

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Accepted for publication March 17, 1954.

[1] Nesbit, R. M. and Glickman, S. I.: The use of glycine solution as an irrigating medium during transurethral resection. J. Urol., 59: 1212–1216, 1948.

within the bottle. The other 2 openings serve as the inlet and outlet for the irrigating fluid. The usual siphon flow is employed for connection to the resectoscope.

The advantages of this system are:

1) The upper bottle may be filled while the surgeon resects tissue since the resectoscope waterway is merely siphoning fluid.

2) Sterility is maintained more easily since only the lower bottle is changed and it is within easy reach.

3) Through the use of a "Y" tube on the ascending filling hose, either one or two bottles can be filled merely by adjusting a clamp. This is of particular advantage in our institution where two transurethrals are carried out simultaneously in the same room.

4) The system can be constructed and put into use with a minimum of effort and expense.

SUMMARY

A simple pressure filling irrigating fluid system was devised at the University of Kansas Medical Center and has been in use for 2 years. This method of supplying a sterile, nonhemolytic solution for transurethral surgery has been extremely helpful to us and is considered worthy of trial by others.

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CLINICAL AND LABORATORY RESEARCH CONCERNING MECHANISMS OF FORMATION AND CONTROL OF CALCULOUS DISEASE BY THE KIDNEY

JOHN EAGER HOWARD

From the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

Ramon Guiteras, whom the American Urological Association has honored by the establishment of this lectureship, was your first president; and his zest for living was evidenced in many spheres. In addition to the publication of a comprehensive treatise on Urology, Dr. Guiteras continuously taught others from his wealth of practical experience over 20 years. He was an expert swimmer, one of the best boxers of his time, a noted big game hunter and a generous philanthropist. It must have been an humbling experience to others, as it is to me, to present to you some simple remarks under the aegis of this great man, whose accomplishments in so many fields few of us can match.

Of Dr. Guiteras' sense of humor, I have been able to glean but little. It may well have had some of the Puckish quality of your present President, who is also a great athlete and lover of the outdoors. But when Dr. Colston flattered me with the invitation to be with you today and himself designated the title for the lecture, he failed to add that at your last meeting there had been a vast symposium on the subject of urolithiasis by experts from a variety of scientific disciplines.[1] I should scarcely have been audacious enough to risk discussing before you a subject upon which basic information is so tenuous, the fundamental mechanisms are unknown, and with which one must therefore deal, having as weapons only some of the peripheral factors which are now visible. Being faced with this situation, one can only do the best he can.

My remarks will be divided into two phases: 1) an effort to synthesize certain factual data into a plausible hypothesis upon which to base further researches into the mechanisms of stone formation; 2) a plea for putting to better practical use that little which is now known and a discussion of certain common errors in the management of renal calculi.

My musings on renal calculi came about indirectly from a primary interest in the metabolism of the skeleton. Most physicians in the past have thought of the bones as mere structural girders, struts upon which the flesh could hang with some rigidity of support and upon which muscles could pull for locomotion. It has only been in relatively recent years that the skeleton has come to be viewed as an active living tissue system, with breakdown and repair going on just as it does in the muscles, liver and heart. The lime salts resident in the bones have been shown to play an exceedingly important rôle in our daily well-being, by acting as a storehouse upon which various mechanisms play so that calcium is either yielded to or accepted from the blood, thereby keeping the amazing constancy of the calcium

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The Ramon Guiteras Lecture read at annual meeting, American Urological Association, New York, N. Y., June 2, 1954.

[1] Panel discussion on urolithiasis. Urol. Survey 4: 1, 1954.

content of the fluids which bathe our cells.[2, 3] Were it not for this function of the bones, we should be constantly at the mercy of our external environment; and, on a day of starvation or when no calcium was available in the diet, we should be in the convulsive spasms of tetany due to hypocalcemia; contrariwise a large meal of calcium would induce hypercalcemia with all its attendant woes. In comparison with the bones, the kidneys and the gut are really small operators in the field of calcium homeostasis, the kidneys being capable of excreting but a gram of calcium per day even in the face of severe hypercalcemic stress.[2]

Bone is composed of lime salts of specific type and character, but it is a cellular structure with *inter*cellular substance of a very special kind, which is called *matrix*. This matrix is composed of protein and polysaccharide substances, *microscopically* identical with the collagen of other fibroblasts, but which clearly differs from collagen in having the property to compel deposition of lime crystals when the surrounding media—i.e., the extracellular fluids—are chemically normal.[4] Furthermore, the crystals are laid down in a definite pattern along the collagen fibres,[5] and it is believed that the *properties of the matrix govern the initiation and orientation of the crystal structure of bone*. You will begin to wonder, what has all this to do with kidney stones? During studies on the matrix of bone, it became apparent that this calcifiable substance contained material with characteristic staining reactions—it was metachromatic to toluidine blue, showing it to be a highly polymerized sugar, and it stained positively (i.e., a pink color) with Hotchkiss periodic fuchsin technique.[6] We were much surprised to find that a *ground substance* with similar staining properties was also present in the deposits of calcinosis in the skin, in tuberculous and arteriosclerotic calcifications, in denta tartar and in *all types of calcific renal stones* except calcium oxalate.[7]

It seems plausible that, just as bone matrix is the initiator and orienter of the skeletal lime crystals, the matrix of *some urinary lime stones* may serve the same purpose, and that the two may be of allied chemical composition.

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b. Follis, R. H., Jr.: Some histochemical observations on normal and diseased cartilage and bone. Tr. 1st Conf. on Metabolic Interrelations, Josiah Macy, Jr. Foundation, New York, Feb. 7–8, 1949, p. 27.

[7] Rubin, P. S. and Howard, J. E.: Histochemical studies on the role of acid muco-polysaccharides in calcifiability and calcification. Tr. 2nd Conf. on Metabolic Interrelations, Josiah Macy, Jr. Foundation, New York, Jan. 9–10, 1950, p. 155.

This audience need not be reminded that renal calculi, like bone salts,[8] are *not* mere precipitates as one sees in simple supersaturated solutions, but are conglomerations of crystals.[9] Under test tube conditions, comparable to those of the urinary tract, precipitations of supersaturated solutions of calcium and phosphorus, or, for that matter, uric acid or cystin are *not* just like kidney stones; for with simple shaking they resuspend in particles which would pass through any reasonable sized tube. Certainly for most stones there must be a binder, or mould or matrix which allows of the growth of or conglomeration of the small crystals initially formed. Such a matrix, similar in at least certain respects to that of bone and cartilage, we found, as just mentioned, in all calcific stones studied that were not oxalate.[7]

It is a reasonable thesis, I believe, that under a *given set of circumstances already conducive to stone formation*, the tendency for such cohesions to occur and enlarge would be enhanced if the principal substance or substances forming the crystals were increased in amount—i.e., *if the head of chemical pressure to precipitate were exaggerated.* Likewise that if the *local conditions* favoring precipitatation were improved—such, for example, as raising the pH of the medium in the case of lime salts or lowering the pH in the case of uric acid—the likelihood of conglomeration would increase. Simple clinical data showing the much higher incidence of stones and the rapidity of their formation in persons whose urine contains calcium in abnormally high quantity, especially if such urine is also constantly alkaline, bear out the relevance of these factors to our subject. And *vicarious calcifications* in usually non-calcifying tissues of the body are also in agreement with such a thesis. For calcification is known to occur in renal tubules under altered physiological conditions of severe alkalosis,[10] and when these tissues are injured by poisons such as mercury.[11] Likewise deposits of calcium are laid down in the lungs, stomach, skin, conjunctivae[12b] and in the environment about joints when abnormally high concentrations of calcium and phosphorus exist in the blood.[12a] Observations on *calcification in vitro* also lend evidence in this direction, for seemingly normal aorta, lung and kidney will show crystalline calcific deposits if left *long enough* in calcium and phosphorus solutions *of greater "products"* (Ca x P) than those which are normally present in the extracellular fluids.[13] Thus many tissues of the body will calcify if abnormal conditions exist conducive to calcification, whereas, of course, they will not if they are uninjured and if the extracellular fluids are normal.

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[8] Neuman, W. F. and Neuman, M. W.: The nature of the mineral phase of bone. Chem. Rev., 53: 1, 1953.

[9] a. Prien, E. L. and Frondel, C.: Studies in urolithiasis. I. The composition of urinary calculi. J. Urol., 57: 949, 1947.

b. Prien, E. L.: Studies in urolithiasis. II. Relationships between pathogenesis, structure and composition of calculi. J. Urol., 61: 821, 1949.

c. Carr, J. A.: The pathology of urinary calculi: radial striation. Brit. J. Urol., 25: 26, 1953.

[10] Cooke, A. M.: Calcification of the kidneys in pyloric stenosis. Quart. J. Med., new series 2: 539, 1933.

[11] MacCallum, W. G.: A Textbook of Pathology. 6th edition. Philadelphia: W. B. Saunders Co., 1936, p. 115.

[12] a. Albright, F. and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease. Baltimore: Williams and Wilkins, 1948, p. 77-79.

b. Walsh, F. B. and Howard, J. E.: Conjunctival and corneal lesions in hypercalcemia. J. Clin. Endocrinol., 7: 644, 1947.

[13] Rosenheim, A. H. and Robison, R.: The calcification in vitro of kidney, lung and aorta. Biochem. J., 28: 712, 1934.

To turn aside now but a few degrees from this line of thought, certain established facts in regard to renal calculi derived from simple clinical data may be noted. Patients suffering from conditions which lead to increased quantities of urinary calcium excretion have long been known to have a far higher incidence of calcific urinary stones than have members of the population at large.[14] Such conditions include extensive immobilization from injury, poliomyelitis or widespread peripheral neuritis, in which atrophy of the bones occurs at a rapid rate, and the lime salts of these bones are poured into the circulating body fluids. Also in skeletal cancer metastases, sarcoidosis, myelomas, Cushing's syndrome, vitamin D poisoning, systemic acidosis and hyperparathyroidism, to name a few. In all of these conditions there is *extensive breakdown and resorption of bone*—indeed I know of no condition in which excessive calciuria exists* in which extensive skeletal breakdown is not concurrent.

When new bone is formed one may often see under the microscope matrix in which lime salt has not as yet been deposited, but during skeletal resorption the matrix invariably disappears, *together with the lime salts;* one never sees bone matrix from which the lime salt has been biologically removed.[16] Whence goes this matrix which has disappeared? It is an interesting thought, though utter speculation, that it or the products of its dissolution may have passed through the blood stream into the urine and *added its force* to the tendency toward lime recrystallization.

By and large the commonest clinical accompaniment of stone formation is urinary tract infection. And it is generally conceded, I believe, that the presence of alkalinizing organisms—i.e., urea to ammonia splitters—are the most obnoxious in this regard. But calcific calculi are still far commoner than coincidence allows in persons with upper urinary tract infections with *non*-alkalinizing organisms. There is something about bacterially contaminated urine which greatly increases the tendency to stone formation *even in the presence of normal concentrations of urinary crystalloids.* All stones which appear to result directly from urinary *infection* are salts of calcium,[1] and all these which we have studied have exhibited a matrix which histochemically appears to be a mucoprotein. Some bacteria in their natural metabolism produce mucopolysaccharides, and one might wonder if some such product of bacterial manufacture could act as an initiator or "matrix" in the formation of urinary calculi. Studies are currently being undertaken with these thoughts in mind.

[14] Ref. 12a, p. 261.

* Possible exceptions to this rule may be: 1) during treatment of hypoparathyroidism with large doses of vitamin D where there is often marked hypercalciuria with normal or even subnormal serum calcium concentrations[15] or 2) in instances of so-called idiopathic hypercalciuria, in which there are no data as to whether *total balance* of calcium is positive or negative.

[15] Howard, J. E. and Connor, T. B.: Some experiences with the use of vitamin D in the treatment of hypoparathyroidism. Tr. A. Am. Physicians, 1954. In press.

[16] Park, E. A.: Bone growth in health and disease. The Leonard Parsons Memorial Lectures I and II. Birmingham, England, 1953. Arch. D. S. Childhood, 29: 269, 1954.

The line of reasoning so far pursued has led to the hypothesis that the deposition of crystalline urinary calculi may be aided and abetted by urinary colloids, acting by some such mechanism as a template to initiate and orient the growth of sizable crystal conglomerations, analogous to the present concept of the mechanism of normal skeletal mineralization. Further pursuit of evidence along these lines may lead us to an approach toward prevention or even dissolution of renal calculi by attacking or disintegrating the *matrix* as well as to dissolve the crystalline components of the stones. In the normal resorption of bone, as well as in pathological states, nature's way is to dissolve *both the matrix and the salts*. Perhaps she does this by first disintegrating the ground substance and the mineral constituents can then be readily disposed of. It is believed by many students of bone physiology that the *bone cells* not only lay down the matrix but also, under different stimuli and circumstances, destroy it as well. We cannot help but feel that if we learn more about how the skeletal tissues lay down and resorb their mineral constituents, we shall have a greatly improved approach toward an understanding of urinary lithiasis. Such an approach toward the problem of renal calculi is not *new or unique with us*, as witnessed by papers on your program two days ago. A somewhat similar line of reasoning led to the recent administration of hyaluronidase in the treatment of nephrolithiasis.[17] But, in the latter, the purpose was *to furnish* the urine with *new colloids* derived from breakdown of collagen —these colloids to act toward overcoming or decreasing the tendency to crystal formation or conglomeration—a more or less diametrically opposite point of view from the approach here outlined. Parenthetically, hyaluronidase does *not* inhibit calcification of rachitic cartilage *in vitro*.[18]

But a belief that a study of calculus matrices should lead us to further basic information on kidney stones is not to decry previous efforts to dissolve and prevent urinary calculi by attempts to increase the *solubility of the salts* of the crystal structures. For these methods have often proved highly useful and successful. One has only to see a sizable renal calculus disappear after correction of hyperparathyroidism or to watch the dissolution of a large cystin or uric acid stone under urinary alkalinization to accept this statement. However, *direct* attack by bathing calculi with chelating materials such as citrate solutions or versene have usually *not* been successful and more often have served to irritate the membranes of the urinary tract as well. Indeed the recent studies of Yendt in our laboratory, indicating that bone matrix may have all its lime salt removed by chelating agents and still be calcifiable when returned to normal serum,[18] would further vindicate a studious approach to the nature of the matrices of kidney stones in the hope of thereby attacking *them* in addition to their salts.

Thus far my remarks have dealt with nebulous and fanciful thoughts, certainly of no value whatever to the physician faced with the *immediate* problem of dealing with a patient full of kidney stones. I mentioned at the outset that very little basic information is *known* about nephrolithiasis, but it is our belief that that little is put to use far too infrequently. I should like to turn now to more practical matters with a brief discussion of the ways and means whereby available information can be best utilized. And the emphasis will be on *simpler* methods of study.

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[17] Butt, A. J., Hauser, E. A. and Seifter, J.: Effect of hyaluronidase on urine and its possible significance in renal lithiasis. J. A. M. A., 150: 1096, 1952.

[18] Yendt, E. R.: Personal communication.

As reiterated many times in your symposium of last year,[1] a knowledge of the *nature* of the stone or stones previously passed by the patient is of inestimable value in one's orientation toward the problem at hand. Most stones are not absolutely "pure" but their major crystalloid is usually apparent from a simple chemical analysis. Yet in not more than 10 per cent of patients seen *even today* have analyses of their previously passed calculi been carried out. We have ourselves been guilty in this regard, with a rude awakening, fortunately not too long delayed, as furnished by the following example. A man had had multiple attacks of renal colic and one large stone had been removed from a kidney before the diagnosis of hyperparathyroidism was finally made by a famous clinic and the offending adenoma was removed. At the time of the patient's discharge from that clinic, the serum calcium had returned to normal and he was no longer excreting excessive quantities of calcium in the urine. A sizable stone was known to be present in one kidney pelvis but was not causing either symptoms or mechanical interference with renal function. However, within a year bouts of colic began to occur on this side and infection supervened, and he sought the help of Dr. Colston at the Johns Hopkins. The large stone appeared not to have increased in size since his parathyroid operation, the infecting organism was not a urea splitter but was resistant to antibiotics *in vitro*, and so the stone was surgically removed. After recovery from the operation, our studies were being carried out along lines of calcium metabolism on the assumption that the stone had been secondary to his hyperparathyroidism and to determine the possibility of the existence of another adenoma. At this point the patient had another renal colic and passed a small stone which he saved. The laboratory technician had been sick for about two weeks and both the small and large stones were analyzed coincidently. To our amazement the small stone was pure uric acid, the large one nearly so with only traces of calcium phosphate. The patient's uric acid metabolism was then studied and he was found to be one of those rare individuals who manufacture endogenously more uric acid than does the normal, but also excretes more, thus maintaining a normal level of serum uric acid. He had the metabolic defect of gout but a compensating kidney which prevented hyperuricemia and made hyperuricuria obligatory. One wonders in retrospect if the hyperparathyroidism had anything *at all* to do with his nephrolithiasis. Had this man's stones not been analyzed, he would have left the hospital with a perfect set-up for repeated colics; as it is now, with reduction of the protein in his diet, drinking large quantities of fluids, moderate alkalinization of the urine—safe, I believe, because he has normocalciuria—the chances of elimination of his painful attacks are very good indeed.

Stone analysis may point the emphasis toward infection as playing the major role in stone formation, even in the face of other adjuvant factors such as hypercalciuria, hyperuricuria or cystinuria. For stones containing much ammonium or magnesium phosphate almost invariably incriminate bacterial forces at play, and one may direct his therapeutic approach accordingly. Actually no type of stone can be identified positively without analysis; gouty subjects may have calcium stones and cystinurics, even severe ones, may live out their lives with no stones whatever or suffer colic from calculi of totally different origin. The technique of simple chemical analysis can be learned quickly by any technician and will often identify the major *visible* offending mechanism and may also give the clue to other factors in instances of mixed stone formers. More highly complex methods of analysis by crystallographic and other techniques[9] of course yield still further information but these procedures are far too difficult for *routine* clinical use.

I should like now to outline certain other studies which have seemed to us of great practical value when carried out routinely and to suggest certain therapeutic implications which may be derived from them. It should be emphasized that *all* these simple methods should be employed, lest discovery of one obvious factor result in complacency and a much more important mechanism in calculus formation be overlooked—as in the instance of our error previously described.

A history of alkali ingestion and *careful* study of urinary pH deserve some comment. Administration of alkalis is not so common now as formerly, yet the public still consumes, for digestive complaints, enormous quantities of powders and tablets which will raise the pH of the urine and thus promote the tendency for precipitation of calcium complexes. Instances are still seen each year wherein the elimination of absorbable antacid powders render patients free of their former repeated attacks of renal colic. In testing for the urinary pH one must be careful that the collecting container has not been cleaned with strong acid or alkali, for a small residue of such solution may completely distort the results. The history should also include careful questioning relative to administration of vitamin D, for it has recently been found that this drug may induce marked hypercalciuria even in the absence of hypercalcemia.[15]

It is wise to carry out bacterial culture of the urine in all stone patients. Most gratifying to the physician is a report of no growth, but one must take care lest the patient was receiving an antibiotic at the time the culture was taken, for growth may have been prevented yet the organism had by no means been eliminated from the urinary tract. To determine the presence or absence of an urea-splitting organism, a very simple maneuver may save the time required for testing multiple specimens and avoid the expensive laboratory procedure. Merely take in two tubes small amounts of known normal sterile urine; to one of them add a few drops of the suspect patient's urine, and leave both tubes overnight in an incubator or even at room temperature. The next morning test the pH of urine from both tubes with nitrazine paper or some other indicator. The control urine may have become slightly more alkaline by loss of CO_2 through diffusion; but if the patient's urine contained an alkalinizing organism, the urine of the second tube will be far more alkaline than was that of the control.

The profession has always taken a gloomy view of the possibility of eliminating urinary infection in the presence of a foreign body in the form of a stone. It has been our opinion that there are some few instances in which this can be accomplished, and perhaps a good many more in which treatment can *prevent* further renal damage and enlargement of the stone. Moderate doses of a drug such as a sulfonamide or one of the mycins, given intermittently for several days at a time, while not eradicating the bacterial organism, nevertheless may annoy him enough so that he becomes a symbiotic rather than an infectious parasite. This is apparently what occurred in several instances in which the bacterial agent was known to be a urea-splitter; while the antibiotic was being administered and sometimes for several days thereafter the urinary pH was much lowered, indicating that the organism was rendered impotent, at least in its capacity to manufacture ammonia.

Test the urine for cystin. The diagnosis of cystinuria is often overlooked, for two main reasons: 1) Cystin is not tested for in the urine, and 2) it is a common *misconception* that cystin stones are always radiolucent. It is a simple matter to assay the urine of every patient with lithiasis, using the crude and nonspecific test with cyanide and nitroprusside.[19] Rarely will this reaction be strongly positive in other than a cystinuric patient unless the urine be old, contaminated and the odor of hydrogen sulfide plainly detectable. If the crude test is positive, one may run the specific and much more complicated quantitative Sullivan reaction[20] on a 24-hour urine. Normal persons rarely excrete more than 40–50 mg. of cystin per day; the cystinuric excretes more than 10 times this much; and we have seen a patient who regularly excretes nearly 2 grams. There is unfortunately no way yet known whereby we can *markedly* alter the cystin content in the urine of a patient with this metabolic error, but the urine can in most instances be kept adequately alkaline and *fluids forced sufficiently* to keep these persons free of calculi. And so far as we are aware, the calculus formation with its tendency to invite infection and destruction of renal parenchyma is the only way in which this disease state harms its owner. In the past two years we have been privileged to see six cystinurics, all of whom had had multiple attacks of colic of previously unidentified cause.

In the therapeutic attempt to reduce the likelihood of cystin or uric acid stone by the use of alkalis, the medical mariner may need all his wisdom to be guided between the Scylla of undertherapy and the Charybdis of clinical alkalosis. It has been rare in our experience to keep the urine of a patient with good renal function alkaline for all of the hours of a day. But accomplishment of alkalinity for 18 or 20 of the 24 hours is far better than none at all and is usually enough to prevent recurrent calculi, particularly if enough fluid is consumed coincidently to require diurnal polyuria and nocturia. In the very servere cystinurics, i.e., those who excrete more than 1500 mg., we attempt to keep the urinary pH as high as 8.0 for most of the 24 hours. When the dosage of alkali required for this has been determined, it is well to check the serum chloride and bicarbonate concentrations to be sure CO_2 combining power is not greatly elevated. Usually, however, any important degree of alkalosis will be reflected in clinical symptoms of lassitude and headache.

As to the choice of alkali, our experience has been limited to the use of sodium bicarbonate and citrate. In the past two years we have used, solely for convenience and palatability, a solution of sodium and potassium citrate and citric acid, devised for other studies by Mr. Harry Eisenberg.* This mixture contains 2 mEq. of base per cubic centimeter and the usual dose suitable for our purpose is 15 to 25 cc taken in a glass of water after meals and at bedtime. For no visible reason, the dose of any alkali required to serve this purpose of urinary alkalinization varies widely from patient to patient, and each case must be tested individually. If the cystinuric or uric acid stone former is for any reason also hypercalciuric or should become immobilized so as to become hypercalciuric, it is probably wise to accept lesser degrees of urinary alkalinity rather than the increased risk of calcific stone formation.

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[19] Brand, E., Harris, M. M. and Biloon, S.: Cystinuria. J. Biol. Chem., **86:** 315, 1930.

[20] Sullivan, M. X. and Hess, W. C.: The determination of cystin in urine. J. Biol. Chem., **116:** 221, 1936.

The urine of every stone former should be tested for its calcium content, whether or not his calculi be calcific. The Sulkowitch test[21] is useful, and if no cloud whatever appears it is fair to concede that the urinary calcium concentration is playing no important role. But it is better to run the chemical analysis on a 24-hour specimen. When one finds more than 200 mg. calcium in the patient's urine, on an ordinary diet, or more than 125 mg. on a diet low in calcium, every effort should be made to track down its cause. As mentioned previously, acidosis, skeletal immobilization, vitamin D poisoning, neoplastic skeletal disease, sarcoidosis, hyperparathyroidism may all cause hypercalciuria. Recently Albright's group has expressed the opinion that certain types of urinary tract infection may result in the excretion of excessive calcium;[22] just how this comes about is difficult to visualize. Fortunately, so-called "idiopathic" hypercalciuria has been *relatively* rare in our stone formers. They are patients, usually recurrent oxalate stone formers, with consistently elevated excretion of calcium due to no *visible* cause. Long-term balance data are rarely available on such patients. The pattern of their metabolic behavior resembles individuals taking large doses of vitamin D, but who have not become hypercalcemic from the drug. Perhaps the idiopathic hypercalciuric patient is one who absorbs relatively more calcium from a given diet than does the normal person, or makes more vitamin D endogenously. In any event, the first important step for the physician is to identify the *presence* of the hypercalciuria; then to seek its cause in the hope of possible elimination.

Oxalic acid calculi have been so far the most difficult to approach by chemical theorization. This substance has such an extraordinary affinity for calcium that when the two are present in very small concentrations they precipitate as highly insoluble calcium oxalate. Little or nothing is known about how oxalic acid gets into the urine but fortunately most such stones occur in patients who excrete *excess of calcium;* the source of the hypercalciuria may be correctible, and the cycle of recurrent calculi thus broken.

Of the simple tests, therefore, which are helpful in the therapeutic approach to a patient with renal calculi, the following have been advocated:

1) Learn the chemical identity of the stone, if possible.

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* This special citrate mixture contains in each litre citric acid 70 gm., trisodium citrate 98 gm. and potassium citrate 108 gm., in a palatable aqueous base.

[21] Barney, J. D. and Sulkowitch, H. W.: Progress in the management of urinary calculi. J. Urol., 37: 746, 1937.

[22] Albright, F., Henneman, P., Benedict, P. H. and Forbes, A. P.: Idiopathic hypercalciuria (abstract). J. Clin. Endocrinol. and Metab., 13: 860, 1953.

2) Make a crude test of the urine for cystin and, if positive, verify this and determine the quantitative daily output with which one must cope.

3) Determine the presence or absence of excessive excretion of calcium and if this is present:

4) Seek its cause in factors which may be responsible for bone dissolution, hypercalcemia and acidosis.

5) Obtain a urine culture and if there is growth, determine the resistance of the organism to various antibiotics and whether or not it is a urea-splitter.

6) Take a careful history in regard to possible antacid powders or vitamin D administration, but this latter can cause hypercalciuria even without hypercalcemia.

In concluding this lecture, certain apologies seem in order. An individual trained primarily in another medical discipline has undoubtedly travelled paths which seem devious to the urologist. Most of what has been said was of highly speculative nature and based upon investigation in the field of skeletal metabolism, yet seems of possible pertinence to problems in the field of Urology. The matters discussed of more practical turn were derived from an experience gratefully acknowledged, furnished by urological colleagues and reviewed in the hope that the author's errors of omission and commission have yielded information from which some may profit.

The privilege of being your speaker today has been warmly appreciated. The only possible regret lies in the society rulings that no discussion is allowed, for your comments, criticisms and suggestions to these remarks would undoubtedly greatly enhance their virtue and would afford the speaker much enlightenment.

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PRESIDENTIAL ADDRESS

J. A. CAMPBELL COLSTON

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Md.

When I received the honor of election to the presidency of this Association, the largest and greatest of its kind in the world, I accepted this honor, certainly the greatest that I shall ever attain, with deep humility and with many misgivings as to my own capabilities to fulfill the obligations of this high office. However, my fears have been to some extent banished by the ever present help and co-operation of the officers and Executive Committee on whom I have learned to depend for the guidance of the many problems which arise and with growing confidence, I can assure you, that these problems now seem minor in character; that the affairs of the Association are in excellent order, although much detailed work, unstintingly provided by the Executive Committee, is necessary to ensure the efficiency of the organization so that all members shall equally share in its benefits and in its responsibilities, and that its progress shall continue.

One of the great privileges of this office has been to attend many of the Section meetings and to listen to their scientific sessions. These programs have been very impressive to me as they have combined studies from experimental laboratories on research work, which are so essential to the progress of our specialty, together with clinical reports on new technical procedures and presentations of difficult diagnostic problems with which various members have been confronted and the methods which have been used to ensure a correct diagnosis and the application of the appropriate therapy. These latter presentations, sometimes referred to, in a rather derogatory sense, as case reports have impressed me as a most valuable part of the Section meetings, and are often of great value to the members, both old and new, when a similar problem should arise in their own practice.

As a guest at the various Sections I have been impressed by the high standards of the scientific programs, both research and clinical, and by the enthusiasm and the friendly spirit exemplified by all the members. If anyone should have any doubts about the future of Urology or of this Association, my advice would be to this individual, visit the Section meetings.

Another obligation which has descended upon me has been the presidential address; this has weighed upon me and has given me considerable distress. When one has read over the addresses of former presidents the constructive thought and suggestions for the progress of our Association are most impressive. Last year at our meeting in St. Louis you were privileged to hear a thought provoking presentation by my distinguished predecessor, Dr George F. Cahill, in which were outlined the advances in the basic sciences which have occurred, particularly in recent years, and their influence on the development of medical science in general and particularly on the training of those young men who have de-

Read at annual meeting, American Urological Association, New York, N. Y., June 2, 1954.

cided to make our specialty, Urology, their life work. This address could not fail to emphasize the truth of the words of Benjamin Franklin when he wrote, "An investment in knowledge pays the best interest."

As most of you know, one of your past presidents, Dr. Elmer Hess, suggested and worked hard to accomplish the centralization of the offices of the Association in the interests of efficiency, and he was instrumental in obtaining the services of Mr. William P. Didusch as Executive Secretary. It had become evident that the growth of the Association and the many details of its organization had placed intolerable burdens upon many hard working secretaries, all of whom at the same time were actively engaged in the practice of Urology. Mr. Didusch, as you know, had previously been in charge of the arrangements for the Scientific and Commercial Exhibits at the annual meetings and his wide knowledge of both phases has been responsible for the efficiency of these essential features of our meetings. By this appointment all these activities are now integrated in a single office and the burdens on the Secretary have been very appreciably lightened. Your present Secretary, who has spent five years in this exacting position, tells me that he has never been more satisfied than with the present efficiency with which the many affairs of the Association are administered. I would like to impress upon all the members to listen carefully to the report of your Secretary who will explain the details of the office and its benefits to the members.

The financial status of the Association is on a sound basis. A special committee met in February to discuss thoroughly this problem and your Treasurer presented at this meeting some constructive suggestions whereby the favorable financial position could be reflected to the benefit of the membership who, after all, own the total assets of the Association. I especially recommend to the membership to hear this report and to consider carefully the proposed recommendations offered as they represent detailed and thoughtful work on the part of the Treasurer both for the preservation of the financial integrity of the Association and for the benefit of each individual member.

When the offices of the Association were established, it became evident that a further integration of activities could be attained by moving the offices of the *Journal of Urology* to suitable space closely adjacent to the Association offices. This move has now been accomplished and will add much to the efficiency of both organizations. As you know, the activities of the Journal and of the Association are closely interlocked and in addition to his duties as Executive Secretary, Mr. Didusch is also Art Editor of the Journal. It is a simple statement of fact that the publication of the Journal is dependent on the intelligent and conscientious work of Miss Bertha M. Trott, the business secretary, and the high standard of its illustrations is due to the careful supervision of Mr. Didusch.

The business affairs and management of the *Journal of Urology* are of paramount importance to each and every member of the Association, because the Journal is our official publication and therefore the property of the members. At some of the Section meetings I have discussed informally the affairs, policies and difficulties of the Journal, but these matters are so important to all of you that, even at the risk of repetition to some, it seems to me that these problems should be presented before the whole membership of the Association.

As you all know, the American Urological Association was founded here in New York City in 1902 and Dr. Ramon Guiteras, whose name we honor by an annual lectureship delivered by one of the outstanding scientists in our country, was elected its first President. The papers presented at the early meetings were published at first in various medical journals. At the convention held in 1907 it was decided that the papers read at the annual meeting, together with discussions and the presidential addresses, be published in a single bound volume. These Transactions continued to appear until the meetings were temporarily discontinued in 1917 because of the war.

At about this same time it became evident that with the growth and expanding interest in Urology a new journal was necessary for the publication not only of papers read at the annual meetings but also papers on urological and allied subjects emanating from individuals who were not at that time members of the Association. Therefore, in 1917, Dr. Hugh H. Young, with his usual foresight, conceived and founded the *Journal of Urology*. At the original meeting which conducted the business arrangements with the Williams and Wilkins Company, in addition to Dr. Young, were Dr. William C. Quinby, Dr. William A. Frontz, Dr. David M. Davis and Mr. William P. Didusch. Dr. Young, with expert legal advice, concluded a contract with the Williams and Wilkins Company which is in force today and which has had far reaching consequences on the finances of the Journal and also indirectly upon the individual members of the Association. This contract provides a journal of 1700 pages per year; all pages in excess of the allotted 1700 costs the Journal in the neighborhood of $20 a page at present. It is therefore obvious that it is of paramount importance that the page limit be not exceeded to any appreciable extent if the financial status of the Journal is to be kept in balance, and this fact is also of importance to the members because any deficit incurred must be made up by the Association and would probably be reflected by increased dues or an assessment on the individual members. The contract also includes the unusual provision that all illustrations accompanying an article will be published at the discretion of the Editorial Board, with no additional charge to the author. I know of no other medical journal which enjoys a similar privilege and the saving to authors is obvious.

At the original meeting Dr. Young was named as Editor-in-Chief. The Editorial Committee consisted of Drs. William F. Braasch, Henry F. Bugbee, Herman L. Kretschmer and William C. Quinby. Dr. William A. Frontz served as assistant editor until his death in 1934. During the ensuing few years the business work was carried out in Dr. Young's private office by his personal secretary and the inevitable deficits incurred were assumed by him. The cost of the Journal to individual subscribers was $7.50 per volume.

No meetings of our Association were held in 1918 or 1919, but in 1920, under the presidency of Dr. Arthur Chute, a most important step was taken leading to the integration of urological activities in this country. A motion was made and passed at this meeting whereby the *Journal of Urology* became the property of the Association and the subscription price was included in the annual dues. This action has cemented the close co-operation between the Association and the Journal, has ensured the financial security of the latter and has made certain that every member of the Association will receive the Journal as a part of his membership dues.

The progress of the Journal has been steady and sure. With the increase of subscriptions, now over 6,000, and as a result of this the increase of lucrative advertisements, the financial status has become more and more stable so that in 1948 it was possible to reduce the cost of the membership subscription to $6.50 per volume in spite of the astronomical rise in labor and printing costs. In the days which we have been through and are going through a reduction in the costs of any commodity seems to me a financial achievement of no mean stature, but you must be aware, gentlemen, that this desirable goal could never have been achieved were it not for the wise contract which Dr. Young engineered, and it should be remembered by all of you gentlemen that the benefits of his foresight, now nine and a half years after his death, in addition to his other achievements in Urology, are still accruing to the Association and to all its members.

After the death of Dr. Young the offices of the Journal were continued in the Brady Urological Institute without charge, due to the courtesy of Dr. William W. Scott, who succeeded Dr. Young as Director of the Institute and it was only when the advantages of integrating the two offices became so obvious that the change was made. It is only fitting here to acknowledge again the debt that we owe to our former President, Dr. Elmer Hess, who deserves the credit for this forward step and also for the adequate compensation of the Executive Secretary and the Art Editor which were achieved during his tenure of office.

Some years ago it became evident that a change should be made in the Editorial Board in order to ensure more equitable representation to all the members of the Association. Now, as you know, each Section elects a member to serve on the Editorial Board so that all Sections are equally represented, as they should be in a democratic organization as is our Association, and take part in forming the policy of the Journal and supervising its operation. These gentlemen are invaluable to us in the editorial office as they are responsible for evaluation of papers read at the Section meetings and for the selection of papers suitable for publication in the Journal.

Selection of papers suitable for publication in the Journal is indeed a great responsibility of the editorial office as, of course, this entails also rejection of papers. As we see our duties, the standard of the Journal must be kept at a high level and papers selected for publication must meet certain requirements. In the selection of these papers the work of the associate Editorial Board, by whose members the papers read at the Section meetings are screened, is essential. In addition, it has been our custom in the editorial office to send certain papers about which we are doubtful and also papers whose authors have written to us protesting their rejection, to the individual members of the associate Editorial Board for their individual evaluation and, of course, we always accept the opinion of the majority.

Rejection of a paper is a serious matter as it is always a disappointment to the author who has often spent much detailed work upon its construction, as I well know from personal experience. J. S. Billings in "An Address on Our Medical Literature" in 1881 sagely stated the criteria for authorship as follows: "First have something to say, say it as briefly as possible and stop when you have said it." To these salient points I would add, read it over at least twice to eliminate mistakes in spelling and grammar and especially verbosity. To an experienced editor it is immediately evident when a paper has been received whether or not the author has reread it and when such is evidently not the case it is very probable that this paper will be looked upon with jaundiced eyes. This is particularly true when the manuscript is accompanied by a long compilation of the literature. Theoretically, at least, when an author quotes a reference from the literature he should have read that particular paper and have been familiar with its contents. Too often we are faced with voluminous references to the foreign literature and it is often difficult for us to decide from the spelling whether the language is Sanskrit or Esperanto. Such a paper is immediately viewed with suspicion because it is only too evident that these references have been collected by a secretary whose knowledge of foreign languages is entirely theoretical.

The use of abbreviations must also be condemned. While B.U.N. and N.P.N., to mention only two of the many which are in common usage, mean something concrete to us today, it must be remembered that in the not too distant future other tests will be developed and perhaps unfortunately other abbreviations will appear. One of the members of our Association, Dr. Alexander B. Hepler, in his presidential address before the Pacific Coast Surgical Association, which is well worth reading by all authors of medical papers, emphasizes this tendency by an example taken from a case report which said, "S.O.B. climbing stairs. We can recognize that shortness of breath was meant, but if the patient had seen it, he might have some cause to question his doctor's friendship. This Morse code may be all right in dressing rooms and staff conferences, but it has no place in a paper or formal discussion." Hepler also protests against the ungrammatical expressions and medical patois and the use of a noun for a verb which appear only too often and quotes Fishbein who states, "The astronomer never telescopes the skies, bacteriologists never microscope their slides, but urologists never hesitate to cystoscope their patients." It is unfortunately all too common to read "pathology showed." Pathology shows nothing as it is defined as "that branch of medical science embracing the knowledge of changes in a living organism induced by disease."

To avoid simple mistakes in grammar, poorly expressed phraseology and especially verbosity, which always implies purposeful padding, revision and then revision again are absolutely essential. One of the members of the New England Section evidently sympathizing with the tribulations of an editor has kindly sent me the following entitled "Cacoëthes Scribendi" by Oliver Wendell Holmes which I shall quote:

"If all the trees in all the woods were men;
And each and every blade of grass a pen;
If every leaf on every shrub and tree

Turned to a sheet of foolscap, every sea
Were changed to ink, and all earth living tribes
Had nothing else to do but act as scribes.
And for ten thousand ages, day and night,
The human race should write, and write, and write,
Till all the pens and paper were used up,
And the huge inkstand was an empty cup.
Still would the scribblers clustered round its brink
Call for more pens, more paper, and more ink."

It is apparent from the foregoing that my sympathies are definitely on the side of brevity, but I recognize also that certain papers, especially those from research laboratories, are necessarily of considerable length if the findings and conclusions are to be adequately presented. To keep within our allotment of 1700 pages per year and thus conserve the financial status of the Journal it has been the custom of the editorial office to request authors of lengthy papers to condense their material whenever possible, and I should like to express my gratitude to all those who have co-operated with us with such good grace. We know full well the sacrifice which this means, not only the additional work which an author, who has spent many hours in the preparation of his paper, must do, but also the regret that he surely has in the radical surgical treatment to which his presentation must be subjected.

Last year the Editorial Board presented to the Executive Committee of the Association a plan whereby it is now possible to publish more of these lengthy papers without condensation. This plan, which was approved by the Executive Committee, provides that if the author will pay for additional pages beyond a maximum determined by the Editorial Board, his manuscript will be published in full. Many of these more lengthy studies are subsidized by commercial firms or emanate from research laboratories with funds available for the specific purpose of defraying the cost of publications so that the expense of publication of these communications rarely will be borne by individual authors. Already, several articles have been published under this plan and when it is in more general use it will be possible to increase appreciably the page space of the Journal without jeopardizing its financial security.

I like to feel that, like so many other American publications, the Journal may be playing some small part in bringing us closer to members of our profession in other countries, and thus to lend some force to international understanding and to lessen the possibility of another cataclysm such as has happened twice in my lifetime.

In 1913 it was my good fortune to take a short trip abroad. That was an era when no passports or photographs were required and the world was peacefully flourishing. Many American physicians traveled to European hospitals and clinics, especially in those days to Germany and Vienna, to observe and many remained for varying periods of time to work in the fields in which they were especially interested. Unfortunately, through the blunders and stupidity of politicians and statesmen and the mad and reckless ambitions of certain rulers, this Pax Brittanica, as it has been aptly named, was rudely broken by World War I. This not only resulted in the massacre of the finest human material in France and Britain and also, of course, in Germany, Austria and Russia, but it brought about that greatest of all tragedies, the Bolshevik Revolution, the effects of which have hung over this troubled world ever since and will continue to affect all of our lives as far as one can see in the future.

During this war it was my fortune to serve some months as medical officer with an infantry battalion and I was no exception to the rule that war for those on combatant assignment consists of a few moments of soul-shaking fear and many periods of morale-destroying boredom. But this duty was essential and many times my thoughts would stray over to my opposite number in a German aid post not so many hundred yards away, who also was dedicated to the relief of suffering among the thousand men under his care. No one but a physician can understand to its full extent the horrors of war from the front line to the hospitals that must be maintained to care for the hopelessly maimed which are its inevitable result.

It has seemed to me that closer relationship and understanding between the physicians of the world might some day prove to be a compelling force in preventing a recurrence of this great calamity which has twice afflicted humanity in such a short time. Therefore it seems of paramount importance that close relations with physicians of other countries be maintained and it should be a source of great satisfaction to all members of this Association to see so many of our confrères from other countries here at our meeting today. Let us not forget that a physician, with the influence that he may exert over his patients, may be a very powerful factor in cementing friendly international relations. It was with this thought in mind that, with the approval of your Executive Committee, I extended an invitation to the Professor of Urology at Moscow University to attend this meeting. So far, no reply has been received and it may well be that your President, in addition to his other honors, is listed by the State Department and with the F.B.I. as a subversive.

Following the defeat in World War I the influence of German medicine suffered a partial eclipse, but work in universities, hospitals and laboratories was soon resumed and with the worldwide sharing of knowledge, which is the characteristic of our profession, we find the name of Domagh, working in the J. G. Farben industries at Elberfeld, as one of the men who has played an important part in the introduction of the sulfa drugs, indeed an epoch in all fields of medical science and especially so, of course, in Urology. Once again, after suffering the terrors of an insane dictatorship, Germany has been utterly crushed and with her country apparently hopelessly divided, faces indeed a bleak future. But I have a firm conviction that once again her medical scientists will emerge from this present chaos and once again contribute to the advance of medicine.

Sir Winston Churchill in his foreword to the first volume of his great work, *The Second World War*, for which he was awarded the Nobel Prize for Literature, writes prophetically "How the English speaking peoples, through their unwisdom, carelessness and good nature, allowed the wicked to rearm." In his foreword to the sixth volume, entitled *Triumph and Tragedy*, he writes "How the Great Democracies triumphed, and so were able to resume the follies which had so nearly cost them their life." Indeed, an ominous appraisal for what may be in store for our troubled world in the foreseeable future.

It seems therefore axiomatic that firm and friendly relations between our country and the other free peoples of the world will be our greatest safeguard and the exchange of ideas between the physicians of the free peoples may be the firmest foundation for the hopes of all mankind for universal and everlasting peace. Steady progress along these lines has already been made and it is my fervent hope that it will continue. For some years it has been the custom of the Johns Hopkins Hospital to exchange surgeons with their opposite members in Guy's Hospital in London. Some years ago this felicitous custom was first introduced by the Peter Bent Brigham Hospital in Boston. In 1952 Dr. William W. Scott spent 2 months at Guy's Hospital while we at the Brady Clinic were fortunate to have with us Mr. W. D. Doherty. This, I believe has been the first exchange on this basis between chiefs of clinics in our specialty, Urology. Similar relationships have been started with Japanese surgical clinics, at present entirely on a unilateral basis.

It has been most refreshing to observe the increasing number of medical congresses that have developed in the past few years between physicians in this country and our neighbors below the Rio Grande. It was my good fortune in October 1951 to attend the Fifth Congreso Americano de Urologia held in conjunction with the Fourth Congreso Mexicano in Mexico City. A number of American visitors were present in addition to urologists from France and Spain and from all of the Latin-American countries. The papers, discussions and moving picture demonstrations were on a very high plane and a visitor could not fail to appreciate the friendly feeling and hospitality which was everywhere offered and one could be certain that mutual understanding was certainly enhanced. The meeting of the American College of Surgeons in Lima during January 1955, should also be a powerful force in augmenting friendly relations with our Latin-American colleagues which, to my mind, is of the utmost importance and may readily be a very considerable factor in more secure international relations. I would strongly recommend to all the members of the Association to attend such meetings whenever possible; you will not find the language difficulty a formidable barrier.

Robert Frost, the poet, has supported his belief in the inalienable right of every man to go to hell in his own way. This perhaps delectable way of terminating our activities and our troubles in this world has a certain definite appeal, especially to many of an independent mind, but we, as physicians, must ever be extremely careful of the particular path that we choose to descend into our own particular hell. Let us not forget that many vitriolic criticisms have been leveled at us in articles in popular periodicals. These diatribes have been based mainly on the sins of a few individuals, distorted by a writer whose sole purpose is to attract the public eye, but nevertheless based to a certain extent on the truth, and the ultimate purpose of these attacks is to undermine the confidence of the public in the medical profession, leading eventually to the introduction of some scheme of socialistic medicine with the resultant opening of many bureaucratic jobs. Socialistic medicine, to my mind, is a misnomer and it should be deleted from our everyday usage. Socialism is a kindly word, indicating a concern for the welfare of all mankind, until one scratches beneath the surface. Thomas E. Dewey has stated, "I do not believe government can run any business as efficiently as private enterprise and the victim of every such experiment is the public. The great tragedy is that once each new experiment in socialism is started it is never possible to unscramble the eggs. . . . It is a curious thing to me how *these people who are always trying to find new things to socialize* are always the same people who are advocating new and larger expenses by government." We must not forget that the first step towards Communism is Socialism and the lessons of the Bolshevik Revolution should always be in our minds. The autocratic government of Russia was succeeded, as you know, by a Socialist government, the top figures of which were strangely reminiscent of the starry eyed idealists who were so prominent in Washington until the advent of the present Administration. In the short time of a few months these deluded, ineffectual, weak dreamers were overrun and mostly liquidated by the present ruthlessly cruel masters of the Kremlin. The use of the word Communism I should also like to condemn. The word would tend to imply the free advantages of all production for each and every member of the community. But, as we see it today realistically, Communism means the concentration of all power and hence the benefits of all production in a small group of ruthless individuals.

The most potent weapon that we in the medical profession possess against Socialism, the forerunner of Communism, is our relations with our patients, with those who have entrusted their welfare and their lives in our hands. It is with our patients that we may build the strongest possible bulwark against bureaucratic medicine and we must never forget that a patient who feels in his heart resentment against his doctor is a potential recruit in the army of those who would foist bureaucratic medicine upon us.

In our relationship with patients we must scrupulously avoid the stigma of the unnecessary operation. My colleague, Dr. Richard W. Te Linde, President of the American Gynecological Association, has recently chosen this topic for an address before an audience of gynecologists in realization of the dangers and the damage which can result to the *profession as a whole from reckless and ill*-considered surgical procedures. Safeguards against criticism on this score are the co-operation of a competent internist in planning any major surgical procedure, strict adherence to the Golden Rule, and the conscience of the operating surgeon.

We must use extreme care in communications to the press and popular periodicals in the hasty and ill-advised premature publication of matters pertaining to medicine, especially in offering to the public undue hope that a "cure" has finally been discovered for any pathological condition, no matter what it may be. So very, very often subsequent studies have shown that the results claimed fall so far short of the promises held out and that many individuals will suffer great disappointment and will harbor resentment against the whole medical profession for extending hope which cannot be realized.

Expenses of a protracted illness are always a threat to any family, but especially to those of low income. The growth of many hospitalization plans and the recognition of this danger by big business, manufacturers and by labor unions in insuring their workers so that they may have adequate hospital care are most encouraging factors in our fight to preserve medicine as it is today.

Now, a brief look at the future of Urology. We must so perfect our diagnostic methods, our treatment and our surgical techniques to such a degree that our conscientious medical colleagues, the umpires, so to speak, in the necessity for specialized treatment for their patients, must be satisfied that their patients, when in their opinion the necessity arises, are safest in our hands both from a diagnostic and from a therapeutic standpoint. Our diagnostic measures have been today developed to such a high degree that it is inconceivable that men not thoroughly trained in Urology would trespass in our field. In the surgery of the genito-urinary tract there may be some overlapping of interest with the general surgeon and particularly with the plastic surgeon, but this, of course, occurs in other surgical specialties. But it is my firm conviction that these minor differences will always be settled between individuals and in various clinics with the ultimate interest of the patient always at heart.

Interesting statistics and very encouraging ones from the standpoint of the importance of Urology in the field of Medicine as a whole have been furnished me by friends at the Mayo Clinic. Of the total number of registrations at this Clinic in 1953, 28 per cent were seen by consultants of the Section on Urology. In other words, in the judgment of the physicians who first saw these patients, who presented various types of diagnostic problems, expert urological advice was deemed necessary in slightly over one-quarter because of evidences of disease of the genito-urinary tract or to eliminate such a possibility.

Therefore we in the specialty of Urology should certainly look to the future in the firm belief that our field will always hold an essential place in diagnosis and in therapy and that its progress, through research studies both from the experimental laboratory and from the field of clinical investigation, will steadily continue. We must continue to keep ourselves thoroughly conversant with all advances in our particular field and with the problems of Medicine in general and never forget that our most potent weapon against bureaucratic medicine will always be the doctor-patient relationship.

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ION-BINDING PROPERTIES OF ELECTROPHORETICALLY HOMOGENEOUS MUCOPROTEINS OF URINE IN NORMAL SUBJECTS AND IN PATIENTS WITH RENAL CALCULUS DISEASE

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Calcium is a component of 90 per cent of all primary urinary calculi and, alone or with magnesium, comprises the greater portion of the total cation content of such stones (Colby; Prien and Frondel; Wardlaw). Recent studies of the mechanisms of biologic calcification (Baker, Reaven and Sawyer; Howard; Boyd and Neuman) have suggested the possibility that calcigerous urinary calculi may originate in the presence of a chondroitin sulfate (Rubin and Howard) or other ion-binding mucopolysaccharides (Meyer). These substrates or "target substances" may not only provide the architectonic framework of calculi, but may determine the nature of their crystalline structure by "extracting" specific components of urine from solution.

A method has been described for recovering the biocolloids of urine by a combination of dialysis, ultrafiltration, and perevaporation (Boyce, Garvey and Norfleet; Boyd and Neuman). The lyophilized dry weights of the total colloids thus recovered have been found to average 0.0902 gm. per 24 hours of urinary excretion for the normal adult, and 0.496 gm. per 24 hours for patients with calculous disease. In every one of 17 patients with calcigerous renal stones the total urinary colloids were 3 to 13 times greater than the average normal. Only 42 to 52 mg. of these biocolloids excreted in normal urine and only 86 to 312 mg. of the biocolloids excreted by patients with calculous disease were found to be soluble in a veronal buffer of ionic strength 0.1 and pH 8.6. Electrophoretic studies of these soluble components at pH 8.6 and 4.5 demonstrated the presence of all the electrophoretically separable proteins present in normal serum. In addition, there were present in the soluble biocolloids of normal urine small amounts of two components (fc-1 and fc-2) with mobilities greater than albumin at pH 8.6, and a complex polysaccharide which was immobile at pH 8.6 and insoluble at pH 4.5 (Boyce, Garvey and Norfleet; Rigas and Heller). A mucoprotein which comprised a considerable portion of the alpha globulin boundaries of normal urine at pH 8.6 was found to retain a negative charge at pH 4.5. A mucoprotein recovered from the urine of patients with calculous disease was found to have a significantly different mobility from the mucoprotein of normal urine at pH 8.6 and at pH 4.5, with a tendency to spontaneous precipitation at the latter pH (Boyce, Garvey and Norfleet).

Further studies with the fractions of the urinary biocolloids which are insoluble

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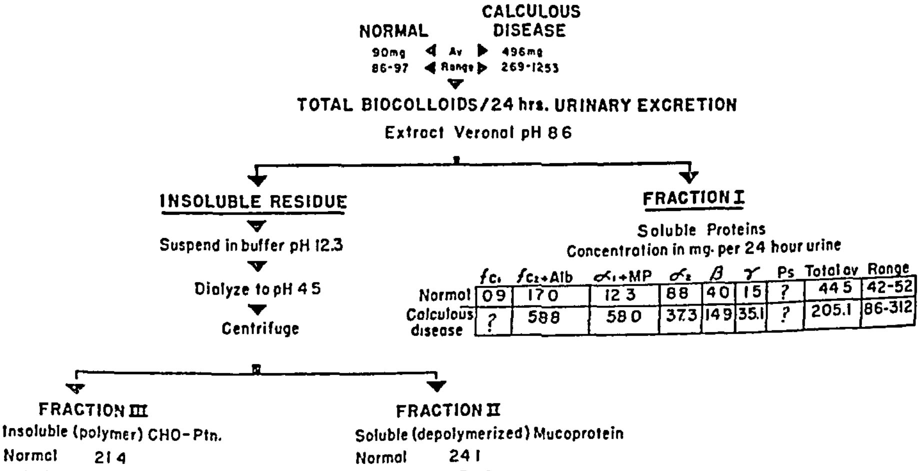
in 0.1 molar veronal buffer at pH 8.6 have demonstrated the presence of another mucoprotein which retains a negative charge over the pH range of 4.5 to 12. In both normal individuals and in patients with calculous disease, therefore, the urine contains at least two colloidal components which retain their net negative charges (migrate toward the anode) in buffer systems throughout the entire pH range of urine. It is the purpose of this report to present data relative to some of the ion-binding properties of these mucoproteins of urine.

METHODS

Isolation of urinary biocolloids. The subjects for this study were 14 normal individuals and 17 patients with renal calculi containing calcium phosphate, calcium oxalate, or both. These patients were selected over a period of 20 months and were demonstrated to have renal calculi of increasing size and to be free of signs or symptoms of actively progressive urinary infection at the time of the study. Seventy-two hour urine specimens were collected from each subject and the total biocolloids recovered by the previously described method. All pH determinations and studies of conductivity and electrophoretic migration were made by previously described techniques. Each 24 hour colloidal residue was extracted three times with ten volumes of veronal buffer, pH 8.6, ionic strength 0.1, and the pooled extracts from each subject were then concentrated by perevaporation or pressure dialysis to a volume of 15 ml. They were then dialyzed for 72 hours against 500 ml of basal salt solution, the solution being changed every 24 hours. These salt-soluble components of the urinary colloids were designated *fraction I*.

The residue from the veronal extraction was suspended in 10 volumes of 0.1 molar veronal buffer which had been adjusted to pH 12.3 with 6 normal sodium hydroxide. This suspension was dialyzed first against distilled water and then against an acetate buffer of pH 4.5, ionic strength 0.1 (Miller), until conductivity studies and pH determinations indicated equilibrium. A precipitate comprising



	f_{C_1}	f_{C_2}+Alb	α_1+MP	α_2	β	γ	Ps	Total av	Range
Normal	0.9	17.0	12.3	8.8	4.0	1.5	?	44.5	42-52
Calculous disease	?	58.8	58.0	37.3	14.9	35.1	?	205.1	86-312

FIG. 1. Method of fractionation of urinary biocolloids. Quantity of each fraction is expressed as milligrams of lyophilized dry material per 24 hours of urinary excretion.

45 to 50 per cent of the original material separated from solution during this dialysis, and was removed by centrifugation. The supernatant from the total 72 hour specimen of each subject was concentrated by pressure dialysis against basal salt solution to a volume of 15 ml. This soluble material has been designated as *fraction II*, and the precipitate as *fraction III* (fig. 1). Fraction III is composed largely of a polymerized form of fraction II, plus a small quantity of material not yet completely identified. All steps in the above procedures were carried out in the cold room at 2 to 5 C.

Incubation in calcifying and noncalcifying solutions. Incubating solutions of the type utilized by Shorr, Goldenberg and others for *in vitro* studies of the uptake of calcium by cartilage were prepared from the stock solutions described by Sobel. The basal noncalcifying solution contained 5 m/Eq. of potassium chloride, 70 m/Eq. of sodium chloride, and 20 m/Eq. of sodium bicarbonate per liter. Ten mg. per 100 ml. of calcium as calcium chloride and 5 mg. of inorganic phosphorus per 100 ml. as Na_2HPO_4-NaH_2PO_4 buffer of pH 7.4 were added for the calcifying solution (table 1). The incubating solutions were prepared by adding the inorganic phosphate to the basal solution, bubbling carbon dioxide through the solution until the pH was lowered to 6.3, and adding the calcium chloride. The pH was then adjusted to 7.3–7.4 by swirling the wide mouthed flasks or bubbling air through the mixture to remove the excess carbon dioxide.

Fraction I from each subject was divided into aliquots of 5 ml. and each was placed in dialyzer tubing 1.89 cm. in diameter which was doubly tied to form a container of this capacity. Each of the samples was placed in a wide mouthed conical flask of 1 liter capacity. Five hundred ml. of basal salt solution was added to one flask, and similar quantities of calcifying solution with phosphate and of calcifying solution without phosphate were added to each of the other flasks. Stoppers containing two stopcocks, one of which extended to a point just above

TABLE 1. *Calcium binding properties of urinary biocolloids at pH 7.4 incubating solution*

Biocolloid	Calcifying with PO_4		Calcifying without PO_4		Basal Salt with PO_4		Basal Salt (Control)	
	Precipitation	Crystal formation	Precipitation	Crystal formation	Precipitation	Crystal formation	Precipitation	Crystal formation
FRACTION I								
Normal	0	0	0	0	0	0	0	0
Calculous	+	+	+	0	0	0	0	0
FRACTION II								
Normal	++	++	++	0	0	0	0	0
Calculous	++++	++++	++++	0	0	0	0	0
FRACTION III								
Normal	Insoluble	0	Insoluble	0	Insoluble	0	Insoluble	0
Calculous	Insoluble	0	Insoluble	0	Insoluble	0	Insoluble	0
CONTROL								
Basal Salt	0	0	0	0	0	0	0	0

the solution, were inserted into each flask and sealed with paraffin. The flasks were thoroughly aerated with a mixture containing 5 per cent carbon dioxide and 95 per cent oxygen, the stopcocks were closed, and the flasks were stored at a temperature of 22 C. Each flask was re-aerated with the carbon dioxide and oxygen mixture at intervals of 48 to 72 hours, and the incubating solutions were changed every five to seven days.

In the first 11 experiments, penicillin (300,000 units), methyl paraben (80 mg.), and propyl paraben (20 mg.) were added to half of the flasks, to prevent the growth of bacteria and molds. Since there was no evidence that these materials had any effect on the results of the experiments, they were added to all subsequent preparations.

As Marks and Shorr have demonstrated, the concentration of bicarbonate used in the calcifying solutions serves as a buffer at pH 7.4 in the presence of an overlying atmosphere of 5 per cent carbon dioxide. Frequent checks of the pH of the incubating solutions indicated that this was maintained most satisfactorily throughout these experiments. The pH of the contents of the cellophane bags was determined at the beginning and at the end of the experiments.

Fractions II and III from each of the subjects were incubated in each of these solutions in exactly the same manner.

In addition to incubating the biocolloids in the basal salt solution, a further control of each group of experiments was carried out by incubating in calcifying solutions both with and without phosphate similar cellophane bags containing, respectively, 5 ml. of veronal buffer of pH 8.0, 5 ml. of 0.1 ionic strength phosphate buffer of pH 7.4, and 5 ml. of 0.1 molar sodium chloride. Cellophane bags containing 5 ml. portions of fractions I and II from 3 normal subjects and from 5 patients with calculous disease were incubated in basal salt solution plus phosphate buffer of pH 7.4, without the addition of any calcium. The insoluble residues left after the veronal extraction of 24 hour colloidal residues from 5 normal subjects were suspended in 5 ml. of basal salt solution, placed in cellophane bags, and incubated in the calcifying solution with phosphate.

Analysis for colloid precipitation and inorganic crystal formation. The flasks were stored at 22 C for 42 days. Any adherence of a precipitate to the walls of the cellophane bag was classified as "precipitation", and recorded in gradations from 0 to 4 plus. The bags were opened to form a sheet of cellophane, and any free precipitate was collected for microscopic study and chemical analysis. The presence of any crystals within this precipitate was recorded as "crystallization," and graded from 0 to 4 plus. The free precipitate was then taken up in 1 to 3 ml. of a 10 per cent solution of hydrochloric acid and qualitatively analyzed for calcium and phosphate.

The cellophane sheets were washed in running distilled water and stained for phosphatic salts of calcium by Von Kossa's technique (Lillie). The presence of calcium was demonstrated by mounting a portion of the cellophane sheets on microscopic slides under water. Buffered ammonium oxalate reagent was allowed to run in under one edge of the cover glass, while water was drawn out with a piece of filter paper from the other edge. The presence of calcium was demon-

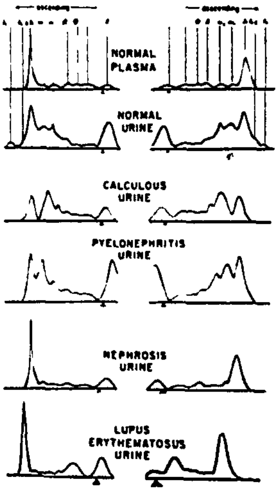


FIG 2

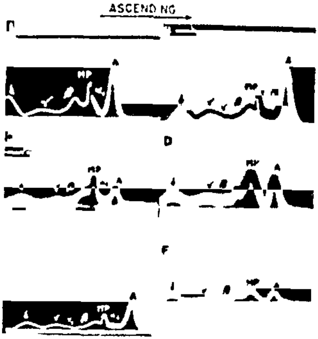


FIG 3

FIG 2 Protein components of fraction I from normal urine and from calculous disease urine as compared with normal plasma and fraction I proteins from patients with obstructive pyelonephritis, nephrosis and lupus erythematosus Latter two pathologic conditions are associated with increased proteinuria as result of altered capillary (glomerular) permeability

Schlieren diagrams obtained from approximately 1 5 per cent protein solutions in veronal buffer, ionic strength 0 1, pH 8 6, following electrophoretic migration at 7 4 volts/cm for 7200 sec at 0 5 C

FIG 3 Electrophoretic patterns of fraction I from 6 patients with calculous disease Protein concentration approximately 1 5 to 2 per cent Veronal buffer, ionic strength 0 1, pH 8 6, potential gradient 7 4 volts/cm for 7200 sec at 0 5 C A = albumin, MP = mucoprotein plus alpha globulins, β = beta globulin, γ = gamma globulin, δ = delta "salt" boundary plus immobile polysaccharide

A and B represent usual patterns encountered in 17 patients Range of observed variations is shown in remaining patterns F Pattern obtained from a patient with primary hyperparathyroidism prior to operation

strated by the appearance of characteristic cubic calcium oxalate crystals This test seemed to be facilitated with 10 per cent acetic acid preceding the ammonium oxalate

The cellophane sheets were then cut into strips, one of which was stained with aqueous toluidine blue (Lillie) and the other with the McManus and Hotchkiss periodic acid technique

RESULTS

Electrophoretic and biochemical characteristics of urinary biocolloids Figure 2 illustrates the electrophoretic patterns of fraction I preparations from healthy subjects as compared with those from patients with calculous disease, obstructive pyelonephritis, nephrosis, and lupus erythematosus Figure 3 shows the characteristic patterns of fraction I preparations from patients with calculous

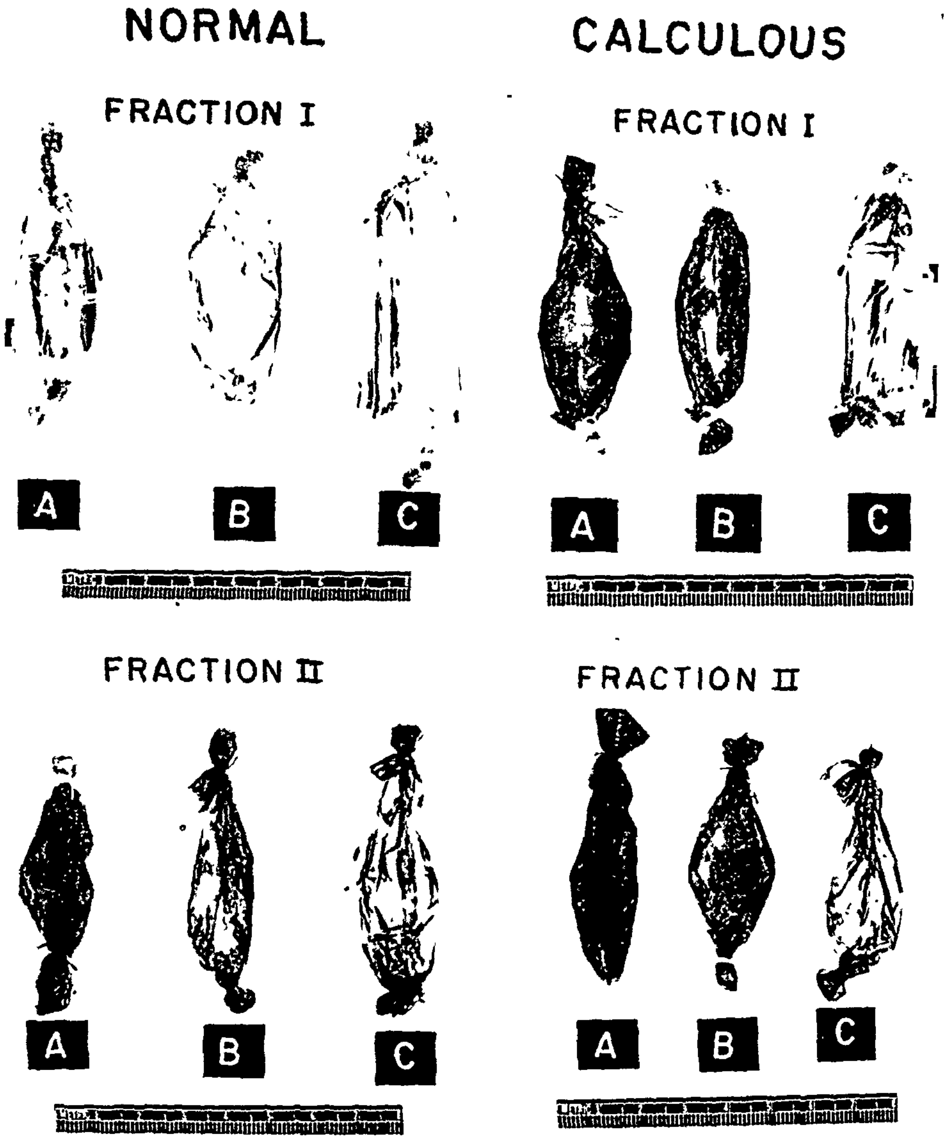


FIG. 5. Mucoprotein precipitation and calcium phosphate crystal formation following incubation of fractions I and II biocolloids from urine of normal subjects as compared with similar fractions from patients with calculous disease. Experiments were conducted simultaneously utilizing same stock solutions to prepare incubating solutions. Incubation period was 42 days. *A*, after incubation in a calcifying solution with phosphate. *B*, after incubation in a calcifying solution without phosphate. *C*, after incubation in basal salt solution.

days. Crystals were not usually observed on microscopic examination of this precipitate, which was so tenaciously adherent to the cellophane that the latter could be washed and stained with no apparent loss of the material.

Crystals appeared as a free precipitate in the dependent portions of the cellophane bags, and were mixed with some organic precipitate. The crystalline material rarely appeared before the fourteenth day, but continued to increase in quantity throughout the remainder of the experiment. Similar experiments prolonged for 150 days have shown a slow but progressive increase in the quantity of crystalline precipitate. Chemical analysis indicated these crystals to be composed of calcium and phosphate.

The larger amount of precipitation and crystallization observed in calculous disease urine probably results from the fact that such urine contains a greater amount of this mucoprotein than does normal urine.

The fraction II preparations incubated in calcifying solutions without phosphate produced a tenacious white precipitate on the inner surface of the cellophane, but no crystallization occurred. Similar preparations, incubated in a basal salt solution containing phosphate but no calcium, showed neither precipitation nor crystallization.

Figure 5 shows typical examples of the fraction I and fraction II preparations after 42 days of incubation.

All of the organic precipitates (fraction I from calculous urine and fraction II from normal and calculous urine) gave a mixture of orthochromasia and metachromasia with toluidine blue, and a positive McManus-Hotchkiss test.

Fraction III. Both fraction III and the insoluble residue from the initial veronal buffer extraction were insoluble in all of the incubating solutions. No crystallization was detected in either of these colloidal residues after incubation in any of the solutions. Since these residues are composed almost entirely of the polymerized form of fraction II, it would appear that formation of crystals is facilitated only in the presence of the depolymerized form of the mucoprotein.

DISCUSSION

It should be noted that certain errors are inherent in the methods utilized for obtaining the absolute values of the urinary proteins shown in the table of figure 1. The quantity of these proteins in fraction I was determined by first obtaining the lyophilized dry weights of the total urinary colloids in 24 hour specimens from 5 normal subjects and from 17 patients with calculous disease. After extraction by veronal buffer the residue was again lyophilized and weighed, and the difference in weights was taken as the value for the soluble portion, fraction I. The values for the individual components of this fraction were determined by planimetry of the projected electrophoretic patterns after the method of Longsworth, and the value for each component was expressed as a percentage of the total. The immobile complex polysaccharide thus contributed to the dry weights of the colloids taken up in veronal buffer but was not included in the planimetric studies, since an undetermined portion of this boundary was composed of the epsilon "salt-protein" boundary which normally occurs in this position. The figure of 17 mg. per 24 hours is greater than the true value for albumin in normal urine, not only because of this "polysaccharide error" but also because a large portion of fc-2 remains included within the area of the albumin boundary. Furthermore, only 90–95 per cent of the refractive gradient which represents the concentration of each individual protein in the final pattern is made up of that specific component, the remaining 5–10 per cent being composed of the immediately adjacent components, thus the planimetric separation of each fraction is somewhat arbitrary (Engel and Catchpole; Reiner, Fenichel and Stern). Nevertheless, the table in figure 1 gives an indication of the relative quantities of these components in normal urine and in urine from patients with calculous disease.

The above experiments introduce problems concerning membrane equilibrium, concerning "salting out" effects of variable ion concentrations on protein mixtures, and concerning the Hofmeister effect of anions on substances which have a tendency to gel—all imponderable factors. The results do not permit unequivocal conclusions as to the role of all, or any one, of these calcium-binding mucoproteins in the origin or development of calcigerous stones. Neither do they establish the mechanism of stone formation to be a recapitulation of the steps illustrated in these experiments—ion-binding, precipitation, and crystallization. Speculation is aroused, however, as to the identity of the urinary mucoproteins and about the factors which may influence their production and activation to a calcium-binding form.

Identity of the urinary mucoproteins. The mucoprotein found in fraction I of normal urine has an electrophoretic mobility at pH 8.6 and pH 4.5 identical with that of Winzler's MP-2 derived from serum. This component along with the other proteins found in serum is therefore most probably a product of glomerular filtration. The component fc-1 was identified as a mucoprotein by Rigas and Heller. The only components detectable in these experiments with mobilities greater than albumin at pH 8.6 were fc-1 and fc-2. The latter may be identical with the mucoprotein of urine isolated by Tamm and Horsfall.

The mucoprotein present in fraction I of calculous disease urine has a mobility slightly less than the mucoprotein of normal urine at pH 8.6, and is isoelectric at pH 4.5 (Boyce, Garvey and Norfleet). This material was identified as a mucoprotein by recovering that portion of it which was precipitated on dialysis to pH 4.5, resuspending the precipitate in veronal buffer of pH 8.6, and subsequently isolating this component from the electrophoretic cell. It was identified as a calcium binding substance by incubating the isolated mucoprotein in calcifying solution in the manner described *vide ante.* Whether this material is a structural modification of the mucoprotein found in normal serum and urine or whether it is derived from some other source—epithelial secretions, for example—remains unknown at present.

It should be noted that the failure to demonstrate fc-1, fc-2 and the mucoprotein MP-2 in calculous disease urine is no evidence that these components are absent in these patients, but only that they are not increased in the same proportion as the other soluble proteins. All the schlieren diagrams were obtained from approximately 1–1.5 per cent protein solutions; thus the individual patterns (figs. 2 and 3) have little quantitative relationship to the total proteins per 24 hours of urinary excretion. A 6 to 24 hour collection from patients with calculous disease was sufficient to give the one per cent urinary protein solutions utilized in the electrophoretic studies. If the small components fc-1, fc-2 and MP-2 had been present in the same concentrations as they are in normal urine, they could not have been detected in such a small quantity of urine.

It is most likely that fraction I from normal urine and from patients with calculous disease includes all of those biocolloids which arrive in the urine by way of glomerular filtration. The epithelial secretions may contribute to this fraction those components not recognizable as constituents of the serum, namely, fc-1, fc-2, the complex polysaccharide which is immobile at pH 8.6, and the alpha mucoproteins of calculous disease urine. On the other hand, *uromucoid* (fractions II and III) in the form in which it is recovered is insoluble in 0.1 molar buffers throughout the pH range of 4.5 to 8.6 and in molar sodium chloride. Hence it is most certainly a secretory product of the epithelial cells lining the collecting portion of the urinary tract. This includes not only the transitional epithelium of the lower urinary tract, renal pelvis and calyces, but also the epithelium of the collecting tubules since the latter have a similar embryonic origin, similar histologic and histochemical characteristics. They are also the principal sites of calcification in nephrocalcinosis.

Factors which may influence the quantity or activity of urinary mucoproteins.

I. Systemic production of mucoprotein abnormal in quantity, structure, or both.
    a. Hyperparathyroidism
    b. Abnormalities of mucopolysaccharide metabolism
II. Local modification of mucoproteins within the urinary passages.
    a. Substances derived by renal excretion.
    b. Direct effects of bacterial metabolism or metabolites (mucinase).
    c. Products of inflammation or repair (epithelial regeneration).
    d. Metabolic alterations of urothelial secretory activity.

The above outline is a purely speculative attempt to correlate some of the phases of mucoprotein metabolism with factors which result in a predisposition to formation of urinary calculi.

The systemic production of mucoprotein implies glomerular filtration as the route by which these materials arrive in the urine. The observations of Engel indicate that parathormone may result in an enormous increase in mucopolysaccharides of serum and urine. The metabolism of mucoproteins is poorly understood, but the monograph by P. A. Levine and the more recent reviews by Karl Meyer indicate the diversity of their metabolic functions. In many instances they appear to serve an architectonic function, and they are components of the secretions from the type of secretory epithelium which lines the ductal systems in which human concretions develop.

Local modification of mucoproteins within the urinary passages implies the presence of these materials in urine either as a result of glomerular filtration or urinary epithelial secretion. Substances derived by renal excretion may influence these mucoproteins within the urinary tract. Baker has indicated that parathormone may directly influence the mucoproteins of the collecting tubules. Hypercalcinuria *per se* should be considered as a possible stimulus in the increased production or activation of urinary ion-binding mucoproteins. Many pathogenic strains of bacteria produce mucolytic enzymes which may depolymerize or otherwise alter the urinary mucoproteins to facilitate the binding of calcium or other ions. Any type of secretory epithelial injury usually promotes increased secretory activity and, by implication, increased production of mucoprotein. It has long been recognized that regenerating epithelium is particularly rich in those materials which stain metachromatically with aqueous toluidine blue (Sylven).

SUMMARY

Both normal urine and urine from patients with calculous disease contain at least two mucoproteins which retain a negative charge throughout the entire pH range of urine. Both of these mucoproteins are markedly increased in the urine of patients with calcigerous renal calculi. Two patients with hyperparathyroidism (functioning adenomas) were found to have the highest concentrations of urinary mucoproteins of any subjects yet observed.

One of these mucoproteins, fraction I, is soluble in buffers throughout the pH range of urine. As recovered from calculous disease urine it has been demonstrated to bind calcium with avidity, forming an insoluble complex. When the incubating solution contains phosphate ions, in addition to calcium, a progressive formation of crystalline calcium phosphate follows the appearance of the calcium-mucoprotein precipitate.

The largest single component of the urinary biocolloids in the normal subjects and in patients with calculous disease is a carbohydrate-protein conjugation joined by polymer linkage to form a compound of high molecular weight. On the basis of the carbohydrate content and the electrophoretic and chemical properties, it is suggested that this material may be correctly referred to as *uromucoid*. The polymerized form is insoluble in molar sodium chloride or in buffers of pH range 4.5 to 8.6, but the depolymerized uromucoid is highly soluble in these solutions. In calcifying solutions the depolymerized uromucoid from both normal subjects and from patients with calculous disease has exhibited ion-binding properties similar to those of the fraction I mucoprotein obtained from the urine of patients with calculous disease.

Some of the factors which may influence the quantity of urinary mucoproteins and their activation to a calcium-binding form have been considered as a background for future investigation.

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DEMONSTRATION OF ALTERED TISSUE MUCOPOLYSACCHARIDES IN RENAL CALCULUS DISEASE BY SELECTIVE STAINING TECHNIQUES

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While various etiologic factors may produce renal calculus disease, the basic mechanism involved in any of them is unknown. Even these etiologic factors are poorly understood. In certain patients, local factors as unilateral Proteus infection or obstructive uropathy are known to have been responsible for stone formation. Most patients with these local factors, however, fail to develop calculi. Nephrocalcinosis or renal calculi are known to develop as a result of gout or hyperparathyroidism. Regardless, many patients with these conditions fail to have calculus disease. These are "known" causes for stone formation. In the majority of patients with stones no etiologic factor can be determined. Randall and Keyser have stated independently that stone formation is a symptom, not a disease. They have elaborated on this thesis by many excellent experimental and clinical observations. In essence, they believed that in many patients stone formation must be preceded by some fundamental change in the urinary epithelium, renal papilla or renal tubule before calcification will develop. For example, it is extremely difficult for Proteus bacilli injected into the rabbit kidney or bladder to produce calculosis unless there has been some previous chemical or physical trauma or foreign body insertion.

Using experimental hyperparathyroidism as a research tool, in previous papers[1, 2] we attempted to demonstrate the modus operandi of this one type of renal calcification, with the hope that the information obtained would provide a clue to the general problem of calculus disease. By carefully quantitating the administered total dose of parathormone it was shown that the earliest calcification began always in the ground substance or mucopolysaccharide of the renal tubule basement membrane. It was demonstrated also that this renal calcification was not due entirely to the effect of parathormone in producing hypercalcemia. Normal rats given large doses of calcium gluconate or dibasic calcium phosphate, and having the same degree of hypercalcemia for the same period of time, failed to develop renal calcification in the ground substance of either the tubule basement membrane or anywhere else in the kidney. These observations supported the concept that there must be renal tissue alteration in order for a calcification factor to become effective.

Altering the condition of the renal tubular ground substance by administra-

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Read at annual meeting, American Urological Association, New York, N. Y., May 31, 1954.

[1] Baker, R., Reaven, G. and Sawyer, J.: Effect of toluidine blue on metastatic calcification. Proc. Soc. Exp. Biol. & Med., 83: 281, 1953.

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tion of anionic dyes, producing renal hyperplasia or administration of desoxycorticosterone acetate (DOCA), resulted in exaggeration or modification of the expected degree of renal calcification from a given amount of parathormone. This phase of the experiment confirmed the work of Rubin and Howard[3] and others[4, 5] that the state of the mucopolysaccharide determines its degree of calcifibility. In conclusion, hyperparathyroidism produces an alteration in the connective tissue ground substance which predisposes this tissue to secondary calcification. This secondary calcification is undoubtedly augmented or accelerated by the hypercalcemia produced.

Certain highly important data to this aspect of the problem of calcification in the urinary tract remain to be developed further. It should be determined whether renal calcification other than that produced in hyperparathyroidism, also has as a necessary prerequisite for calcification an alteration in connective tissue mucopolysaccharide. In addition, no data have been published concerning experimental or human renal calcification in which histologic stains have been utilized for selective study of mucopolysaccharides.

METHODS

A. Staining techniques. Research in this area of urolithiasis has been obstructed greatly by lack of appropriate technical methods. In the present study a variety of histochemical stains were tried and discarded due to nonspecificity or failure of reproducibility. Three stains were finally selected and used in every phase of these experiments.

1) Von Kossa: The tissue is fixed in 10 per cent formalin, dehydrated and later passed through several changes of distilled water. It is next immersed in 5 per cent silver nitrate for 10 to 60 minutes. In our experience 30 minutes is adequate. Next the tissue is washed thoroughly in 2 to 3 changes of distilled water. It is then exposed to sunlight for a number of hours. We have found that immersing the tissue in ordinary photographic developer for a few seconds is a far shorter and equally effective procedure. When the tissue turns to dark brown, it is then removed from the solution and washed well in distilled water. It is next treated for 2 to 3 minutes in a 5 per cent solution of aqueous sodium thiosulfate solution. Following another water wash it is counter-stained for 20 to 60 seconds in a solution of 5 per cent aqueous safranin O. It is next dehydrated in 95 per cent and 100 per cent alcohol. The tissue is cleared in xylene and then mounted in clarite.

2) Polysaccharide stain (Hotchkiss): This stain, as described by Hotchkiss[6] is specific for polysaccharide structures in fixed tissue preparations. It is based on the unique properties of the oxidant, periodic acid. Periodic acid attacks

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polysaccharides, converting them to high molecular aldehyde compounds. These polyaldehydes are then stained easily with fuchsin-sulfurous acid. High molecular substances as polysaccharides, hyaluronic acid, mucoproteins, mucins, are in adequate amounts to give visible color.

The method consists in using the routine fixative of 10 per cent formalin for 24 hours and dehydration. Next immerse gradually to a 70 per cent alcohol solution. The tissue is then left for 5 minutes in periodic acid and rinsed with 70 per cent alcohol. A reducing rinse is used for 5 minutes and following this the tissue is again washed in 70 per cent alcohol. Next the tissue is immersed in special Schiff's reagent* for 15 to 45 minutes. It is then washed 2 or 3 times in sulfite water. The section is dehydrated and mounted in the usual manner.

3. Polysaccharide-phosphate* carbonate stain (Sison): The Von Kossa stain is ideal for the tissue demonstration of phosphates-carbonates. The mucopolysaccharide stain adequately demonstrates normal and altered mucopolysaccharides. Neither of these stains overlaps the other, i.e. they are mutually selective and exclusive of each other. In an effort to correlate the changes in mucopolysaccharide with the deposition of phosphates-carbonates in renal connective tissue matrix, the following technique has been devised and is now reported for the first time:

The block of tissue is fixed in 10 per cent formalin, dehydrated and passed through several changes of distilled water. It is next immersed in a solution of 5 per cent silver nitrate for 30 minutes. Following this it is washed well in 2 to 3 changes of distilled water. It is then immersed in photographic developer for a few seconds until the tissue turns to a brown color. After washing well in several changes of distilled water it is treated for 2 to 3 minutes in a solution of 5 per cent aqueous sodium thiosulfate. It is next washed in water and placed in 70 per cent alcohol. The tissue is then immersed for 5 minutes in periodic acid and rinsed with alcohol. Only 5 minutes is required in the reducing rinse, after which it is washed again with 70 per cent alcohol. Schiff's reagent is used for 15 to 45 minutes. After a final washing of 2 to 3 times in sulfite water, the tissue is dehydrated and mounted in the routine manner.

B. Materials studied by foregoing method. In each part of the following experiments, a sufficient number of rats were used to quantitate the stone producing effect. In some instances this required only 5 rats per group, while in others, significant results were obtained only by using 15 to 30 rats per group. These rats were all of the same strain and weighed 150 to 200 gm. each. All experimental animals were divided into two groups, male and female. The rats were maintained on a uniform, standard, complete diet.

1) Quantitation of the parathyroid effect was performed in the following manner: An amount of parathormone was given for a two week period (500 units total dosage) which failed to produce calcification. The dose was increased in different series of rats, one group receiving 1000 units and another 1700 units.

2) Oxamide has been known to produce experimental renal calcification since

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* Special Number 3 Schiff's reagent obtained from Arthur H. Thomas.

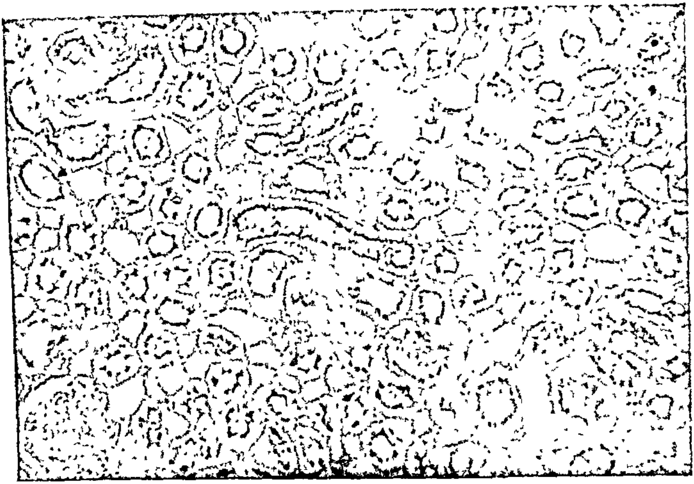

FIG. 1. Polysaccharide stain (Hotchkiss) demonstrating even distribution of ground substance throughout normal kidney. Mucopolysaccharide appears as consistently well defined linear content of basement membrane and surface margin of tubule epithelium.

1891.[7] Rats in this series were tube fed various amounts of an aqueous suspension of the insoluble oxamide. A daily dose of less than 0.1 gm. oxamide for 2 days failed to produce calcification. Subsequent groups received less than 0.2 and less than 1.0 gm. of oxamide daily for 5 days. All rats were sacrificed 2 days after the last dose of the compound.

3) Another group of rats was given 1.0 gm. of uric acid daily for 12 days.

Human materials studied: Three patients having renal calculi or renal calcification were studied. Two of these patients had proven calcium oxalate stones and one had a large staghorn calculus proven to be of cystine composition.*

RESULTS

The normal renal mucopolysaccharide content and pattern is presented in figure 1. The distribution and intensity of the mucopolysaccharide was uniformly constant throughout all normal kidney sections studied. The glomerular tuft was rich in mucopolysaccharides. Bowman's capsule contained an even, regular, lineal amount of mucopolysaccharide. The basement membrane of the renal tubules also had an even, constant distribution of this ground substance. The surface border of the tubule epithelial cells contained as much mucopolysaccharide as the basement membrane. As judged by its greater intensity of staining, the brush border of the proximal tubule contained more mucopolysaccharide than the basement membrane.

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[7] Ebstein, W.: Uber die Experimentelle Erzengung von Harnsterinen. Wiesbaden: J F. Bergmann, 1891.

* The authors are grateful to Dr. Herbert Goldberg of the faculty of Georgetown University for providing the renal tissue from two of these patients.

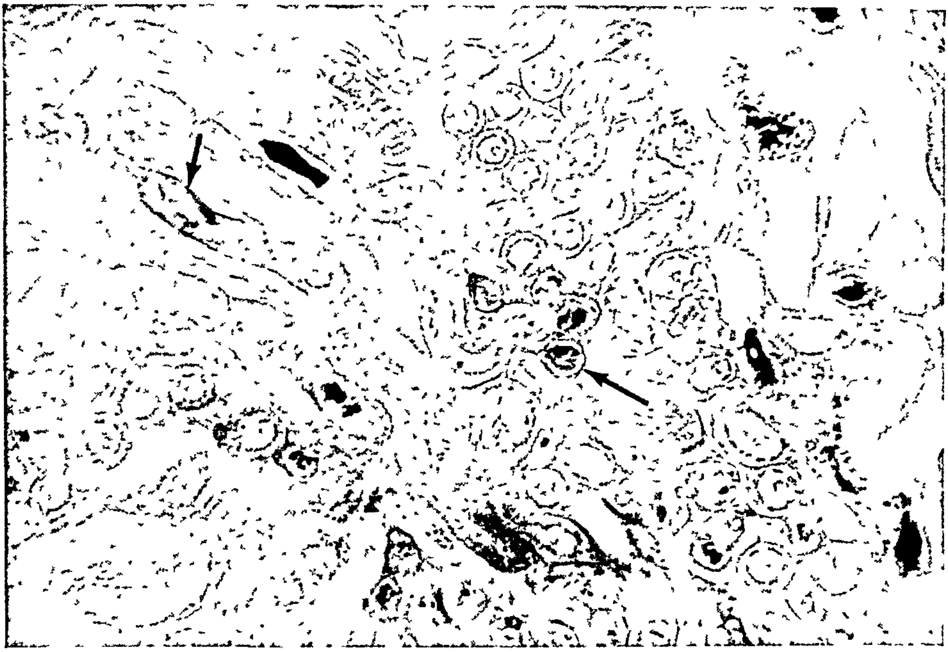

Fig. 2. Polysaccharide stain demonstrating patchy increase in ground substance of renal tubules (arrows) which routinely precedes calcification produced by administration of parathormone (500 units).

By means of the Von Kossa, polysaccharide, and the new procedure described which simultaneously combines features of both these stains, it was possible to confirm and extend our previous impression that the administration of parathormone produces renal calcification in altered mucopolysaccharide of the renal tubule basement membrane and other ground substance of the tubule. Calcification or alteration of mucopolysaccharides was not observed in the glomeruli. In addition, it was determined that ineffective amounts of parathormone (a quantity insufficient to cause calcification) produced marked alterations in the normal mucopolysaccharide of the kidney (fig. 2). The general microscopic picture of these kidneys was a patchy, localized increase in ground substance throughout the entire cortical and medullary segments of the tubules. In the brush border of the proximal tubules, the ground substance was markedly increased over normal. In this ineffective dose range the alterations involved only the basement membrane, but with effective doses of parathormone, it resulted in involvement of the entire tubule epithelium. Subsequent calcification developed or involved only this altered tubule mucopolysaccharide (fig. 3).

A total dose of less than 0.2 gm. of oxamide failed to produce calculi or nephrocalcinosis, but did produce marked precalcific alterations in tubule ground substance (fig. 4) characterized as an irregular, patchy increase in mucopolysaccharide of the tubule epithelium. This involved the basement membrane, surface of the cells and frequently the cells themselves contained polysaccharide staining material. Some of this material was observed in the lumen of the tubules. These changes were noted to occur in small groups of tubules, particularly at the corticomedullary junction. Increased amounts of oxamide caused the production of

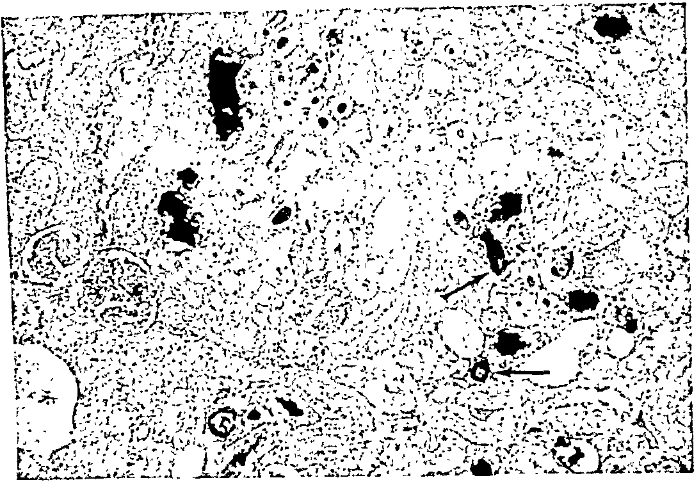

FIG. 3. Administration of 1000 units of parathormone has produced nephrocalcinosis. Sison stain demonstrating patchy increase in tubule mucopolysaccharide and deposition of calcification within matrix (arrows). Glomeruli are uninvolved in process.

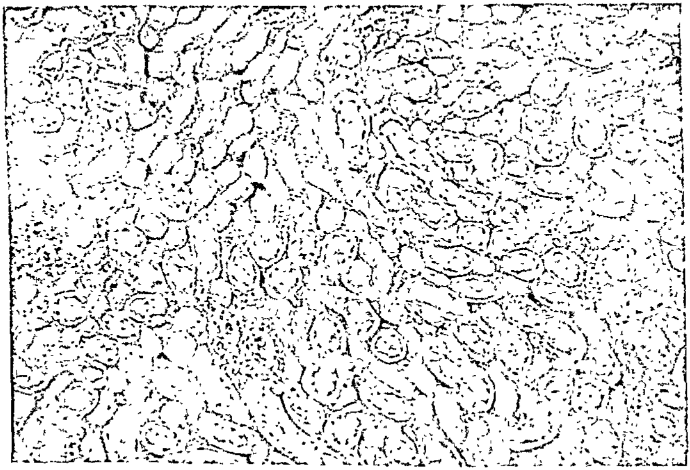

FIG. 4. Precalcific phase of oxamide administration demonstrating patchy increase in tubule mucopolysaccharide by Hotchkiss stain.

calcification to appear mainly within the lumen of the tubules, but some was confined to the basement membrane or the tubule cells themselves but only in areas of altered ground substance (fig. 5). Most rats that developed calcification had stones in the renal pelvis or bladder and some had gross hematuria. One

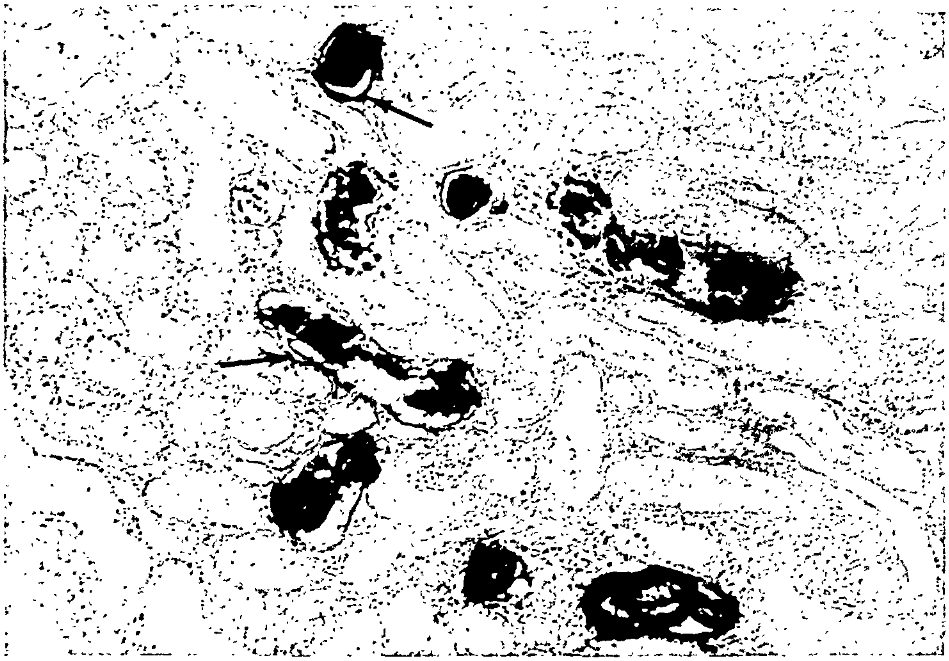

FIG. 5. Calcific phase of oxamide administration simultaneously demonstrating, by Sison stain, calculi within lumen of numerous tubules and its deposition within altered mucopolysaccharide.

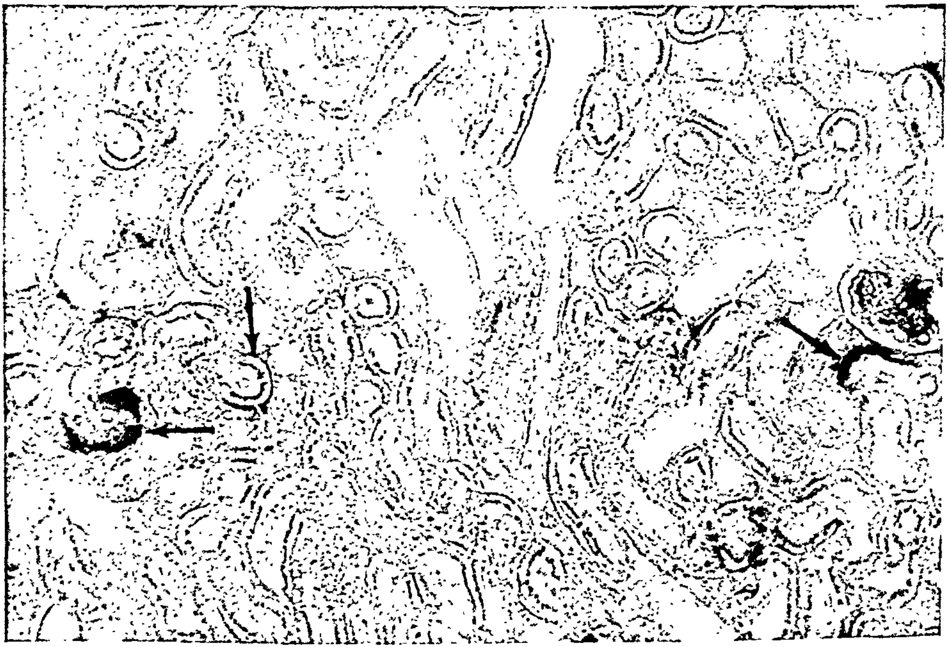

FIG. 6. Demonstration of irregular alteration in tubule mucopolysaccharide produced by uric acid (arrows). No crystals in this section.

calculus was adherent to a renal papilla. The glomeruli were uninvolved with regard to ground substance changes or calcification.

Most rats given large amounts of uric acid failed to produce uric acid crystals or stones. All rats, however, had similar alteration of tubule mucopolysaccharide

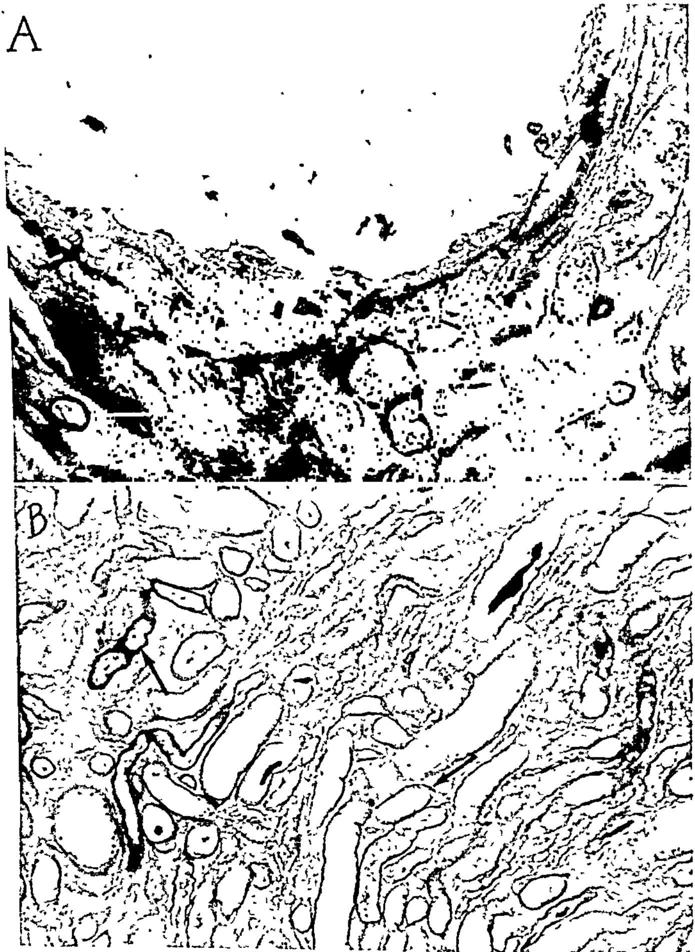

FIG. 7. *A*, human kidney containing staghorn cystine calculus stained by Hotchkiss technique. Section demonstrates cystine crystals adherent to papilla and in some tubules. Marked, patchy increase in tubule mucopolysaccharide (arrows) which appears beneath epithelium. *B*, area of same kidney that does not contain cystine crystals demonstrating patchy increase in tubule mucopolysaccharide (arrows) and polysaccharide staining material within tubule lumen.

as that observed in the parathormone and oxamide experiments. There was a patchy, irregular increase in mucopolysaccharide throughout the entire cortical and medullary parts of the renal tubules. The glomeruli were in no way affected. All changes were in the form of increased ground substance with regard to both

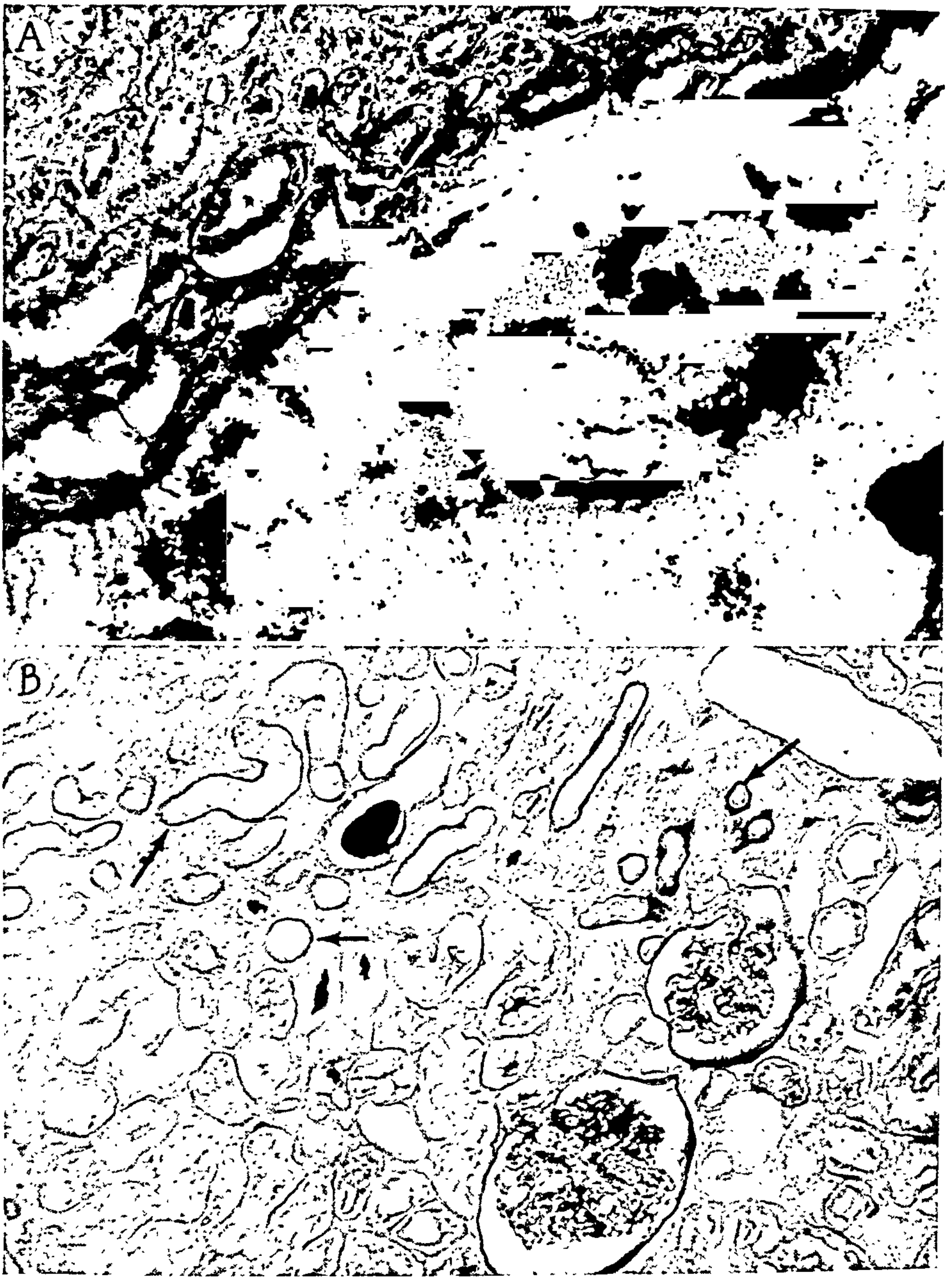

FIG. 8. *A*, human kidney containing calcium oxalate calculus adherent to papilla. Sison stain simultaneously demonstrating attached stone and irregular increase in tubule mucopolysaccharide. *B*, section of kidney shown in *A* stained by Sison technique. Stone demonstrable in renal tubule. Note patchy increase in renal tubule ground substance in those tubules not containing calculus (arrows). Glomeruli contain normal quantity and distribution of mucopolysaccharide.

intensity and distribution. At the dose level of uric acid used, the ground substance alterations were unpredictable. In certain sections the alterations of mucopolysaccharide were so great that it was difficult to determine precisely in what area of the renal tubule they began. In other sections only the basement membrane had increased mucopolysaccharide. In still others, the basement membrane ground substance and also the ground substance on the surface of the epithelial cells were involved in the process. Some sections revealed the entire renal tubule epithelium, which included the cell as well as the cell surface mucopolysaccharide and basement membrane ground substance, to be diffusely involved with increased ground substance. Many tubules demonstrated marked cellular destruction with desquamation and casts within the lumen (fig. 6). Scattered clusters of tubules were packed with red blood cells. All uric acid crystals were deposited in vast clumps only in tubules having marked changes in intensity and distribution of ground substance.

Human sections studied. Cystine calculus: Figure 7 demonstrates the extreme alterations in distribution and intensity of mucopolysaccharide in this human kidney containing a large staghorn cystine calculus. This consisted of diffuse changes of the tubules, many of which were completely destroyed. The alterations were always on the side of an irregular increase, rather than decrease, of ground substance in the basement membrane, the epithelial cells and the ground substance of the surface of the tubule epithelium. This was a generalized increase in staining intensity and distribution rather than the patchy type of alterations observed in the experimental studies. In no sections were the glomeruli involved in these changes.

Calcium oxalate: The alterations of ground substance in these kidneys are demonstrated in figure 8. As in the previous patient with cystine calculi, the two kidneys studied revealed a diffuse increase in mucopolysaccharide of the renal tubules. Specifically, it consisted of an increase of the staining intensity and distribution of the mucopolysaccharide in the basement membrane of the tubules. In many areas it also involved the epithelial cells and their surface ground substance. In no sections was there any detectable difference in either distribution or intensity of ground substance of the glomeruli.

DISCUSSION

Using specific staining techniques it has been possible to determine that the normal distribution of mucopolysaccharide in the kidney is regular and of constant intensity and distribution in the glomerular tuft, Bowman's capsule, basement membrane and surface of the tubule epithelium. The administration of an amount of parathormone that failed to produce calcification (ineffective amount) caused a significant, marked, alteration in renal tubule mucopolysaccharide. This change was characterized by a patchy increase in tubule ground substance while the glomerular pattern remained unchanged. Use of the Sison stain revealed that increasing the amount of parathormone administered caused the deposition of calcification to be localized only in the altered and increased tubule ground substance. No calcification developed in the glomeruli. As no other procedure or compound was performed or administered to these rats, it would be reasonable to conclude that the parathormone first produced the observed precalcific renal ground substance alterations and thereby specifically prepared these geographical tubule sites for the calcification that subsequently developed.

Lack of this prerequisite alteration of renal tubular ground substance necessary for calcification offers a reasonable explanation for the failure in previous experiments[2] to produce nephrocalcinosis in rats during the same time period solely by causing hypercalcemia.

While Ebstein demonstrated in 1891 that oxamide selectively produces renal calcification, it has not been proven previously whether or not this calcification involves connective tissue, glomerulus or renal tubules. Based on the sections studied, it would be unwise to state that calcification appeared first in the basement membrane. The data now presented do indicate, however, that oxamide produces marked alterations in intensity and distribution of ground substance of only the renal tubules. Tubule calcification involved these areas. The administration of an amount of oxamide that failed to produce calcification resulted in these same qualitative tubular changes but were quantitatively less marked in degree. Oxamide did not alter the ground substance or produce calcification in the glomeruli.

It was determined that by the method used that the development of uric acid crystals in the kidney was unpredictable. Regardless of whether or not crystals were produced, uric acid was extremely toxic to the tubules. Scattered clusters of tubules showed a patchy increase in renal tubule ground substance which involved one or all of the following: basement membrane, surface ground substance of the tubule epithelium or tubule epithelial cells. Again, renal tubule mucopolysaccharide changes preceded the appearance of crystal aggregates in or among the tubules. In no instance was the glomerular ground substance altered in quantity or distribution. The results obtained by these experiments appear to indicate that renal tubule ground substance alterations definitely preceded the appearance of crystals. It would also tend to exclude the possibility that the development of crystals and calculi in the renal tubules is responsible for the tubular changes demonstrated.

While there was no observed sex difference in ground substance alteration in these experiments, the number of rats used in each group was occasionally too small to permit valid statistical analysis of this aspect of the problem.

Studying renal tissue from patients with calcium oxalate and cystine calculi, the alterations in renal ground substance, as determined by specific staining techniques, were comparable to those observed in the three methods used to produce experimental renal calcification. In general, there was a marked increase in tubule mucopolysaccharides. This involved the basement membrane, often the tubule cells themselves and usually the surface ground substance of the epithelial cells. In no instance was there any evidence of altered ground substance or calcification in the glomeruli. These changes were the same regardless of type of calculus produced.

In the experimental study and preliminary human report now presented, renal calcification or calculi is entirely a tubule disease. There is no evidence that the glomeruli are involved in any manner in this condition. Altered tubule mucopolysaccharide precedes the development of experimental renal calcification. Subsequent calcification is deposited only in these areas of altered ground substance. As it is probably impossible to obtain sections of human kidneys that will eventually undergo calcification, it is not possible to determine at this time whether in the human the changes in tubule ground substance are the cause or the result of the urine supersaturated with a particular crystal still in solution, or crystals or stones within the tubules. Experimental renal calcification as produced by three different methods supports the previous view. An ineffective amount of parathormone, oxamide or uric acid failed to produce renal calcification, crystals or stones. Yet these three compounds produced selective tubule mucopolysaccharide alterations which were identical in kind, but of less degree, as observed when effective amounts of these compounds were given. Keyser and Randall have independently stated that renal stone formation is not a disease but a symptom. It is probably valid at this time to extend this observation and state that renal stone formation is a symptom of specifically altered tubule ground substance.

The ground substance of renal connective tissue is organized as a highly polymerized carbohydrate-protein complex. This state of organization of ground substance is extremely plastic.[8] While the tissue mucopolysaccharide is considered as insoluble, depolymerization can result in a breakdown to smaller, more soluble residues as mucoprotein.[9] These experiments indicate that there are precalcific alterations of mucopolysaccharide. This was shown by utilization of the polysaccharide stain of Hotchkiss which is based on the unique properties of periodic acid. It should be stressed that periodic acid is not specific for a particular polysaccharide, but demonstrates equally well mucoproteins, hyaluronic acid, mucins, and related high molecular polyaldehydes. It is quite probable that the altered polysaccharide observed in these experiments and in the human kidneys studied, are not normal but are breakdown or depolymerized tissue mucopolysaccharides which have similar characteristics when combined with periodic acid. While the demonstration of polysaccharide by the Hotchkiss stain is crude from the quantitative and qualitative standpoint, it does demonstrate alterations from the normal pattern of intensity and distribution of renal mucopolysaccharides. The changes in renal tubule ground substance presented in this paper appear to be intimately associated with calcification or stone formation. All changes in renal ground substance, however, are probably not specific for subsequent calcification. Undoubtedly diseases such as glomerulonephritis, most cases of pyelonephritis and many other conditions unassociated with renal calcification will produce a change in renal ground substance.

Calcium becomes concentrated in connective tissue in both ionic and protein-bound states. The connective tissue matrix has a negative charge[10] and calcification results in an interaction of the calcium or other electrolytes with the anionic mucopolysaccharide of the renal tubule connective tissue. The three methods described of producing experimental renal calcification or stone formation resulted in altered mucopolysaccharide of the tubule. Use of a combination of Von Kossa and polysaccharide stains has permitted, specific localization of calcification in this altered mucopolysaccharide.

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[8] Gersh, I. and Catchpole, H. R.: The organization of ground substance and basement membrane and its significance in tissue injuries, disease and growth. Am. J. Anat., 85: 457, 1950.

[9] Catchpole, H. R.: Serum and tissue glycoproteins in mice bearing transplantable tumors. Proc. Soc. Exp. Biol & Med., 75: 221, 1950.

Engel[10] has demonstrated that depolymerization of ground substance leads to the formation of *soluble* mucoprotein fractions. He has reported an increase in the urinary excretion of the mucoprotein virus—hemagglutination—inhibiting factor under these conditions. We have observed that in experimental and human renal calcification in which the tubule mucopolysaccharides are presumably depolymerized, that there are frequent polysaccharide staining casts within the lumen of the tubules, confirming Engel's observation relative to the solubility of these fractions. The tubule cells frequently contain mucopolysaccharide. On the other hand, the glomerular ground substance remains unaltered or polymerized in experimental and human renal calcification, and as a consequence mucopolysaccharide staining material has not been observed within Bowman's capsule. In pilot experiments it has been possible to demonstrate an increase in serum mucoprotein (Winzler method) in patients with renal calculi. This will be reported in a later paper.

It would appear that at least two factors are necessary for development of certain types of renal calculi or nephrocalcinosis: first, a preparatory alteration of renal tubule ground substance of a specific type and maintained for an unknown duration of time; second, a constantly available supply of bindable calcium. Miller[5] and Sobel[11] have demonstrated that calcification depends not only on the presence of bindable calcium, but if phosphate is not present, no calcification occurs. Calcification requires the simultaneous presence of both ions. Rubin and Howard[3] have proposed that the mucopolysaccharide may effect its action by a cycle of calcium binding followed by dissociation and recombination with phosphate.

CONCLUSIONS

Experimental renal calcification or stone formation has been produced by parathormone, oxamide and uric acid. The associated changes in renal ground substance have been studied by mucopolysaccharide, Von Kossa and a combination of these two stains. An amount of each of these compounds which failed to produce calcification or stone formation within the rat kidney, produced a patchy increase in tubule mucopolysaccharide which was identical in kind, but not degree, as when an effective calcifying amount of these compounds was administered. Crystals or calcification subsequently was deposited only in these areas. It would appear, therefore, that the changes or alterations observed in renal tubule mucopolysaccharides were not due to tubule injury produced by crystals or stones in the tubules, but rather the renal tubular ground substance alterations necessary for subsequent calcification.

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[10] Engel, M. B., Joseph, N. R. and Catchpole, H. R.: Experimental studies in the calcification and dissolution of bone cartilage. Paper read before Chicago Rheumatism Society, October 28, 1953.

[11] Sobel, A. E., Goldfarb, A. R. and Kramer, R.: II. Role of "local factor" of viosterol in the pathogenesis of rickets due to beryllium. J. Biol. Chem., 108: 395, 1935.

A study of the renal ground substance in two patients with calcium oxalate stones and one patient with cystine stones, also revealed a marked alteration and increase in tubule mucopolysaccharide which was similar to that observed in the experimental study.

In neither the experimental production of renal calculus disease nor in the patients studied were the glomeruli involved by alterations in connective tissue ground substance or with calcification. Renal calculus disease is apparently entirely a tubule process.

A new stain is described for the simultaneous identification of renal calcification and ground substance.

It is a pleasure to acknowledge the technical assistance of Miss Lucy Fang.

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MODIFICATION OF URINARY SURFACE TENSION BY ORAL GLUCURONIC ACID: ITS APPLICATION IN PROPHYLAXIS OF URINARY CALCULI

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The problem of recurrent renal calculi remains one of the most important in Urology despite the momentous strides of the past few years. Higgins, Flocks and Suby have done much to emphasize and popularize the importance of dietary and urinary pH regulation in the prevention of recurrent calculi. Shorr and Marshall have presented what appears to be the answer to the major part of the distressing problem of stone formation in alkaline urine with a resistant urea-splitting infection, by utilizing a combination of low phosphorous diet and aluminum gel. Butt proposed the effect of parenterally administered hyaluronidase on the excretion of protective urinary colloids. Prien obtained the precise constituents of urinary calculi through x-ray diffraction and polarized light transmission. These authors are among those who have bestowed on us the measures for clinical control and the stimulus for further investigations into the problems of urinary calculus formation and prophylaxis.

Despite these various approaches many patients who have been relieved of calculi, spontaneously or surgically, continue to be intermittently distressed by recurrences. When urinary obstruction exists, with or without infection, or when there is a marked excess in the crystalloid elements of the urine, these recurrences are understandable. It is the individual who passes a calculus and who on investigation is found to have an obviously normal urinary tract, without infection and without obvious metabolic dysfunction, who presents a puzzling situation. This type of person, without a special diet or specific treatment, may go for years without forming another calculus. On the other hand, there may be a recurrence in a year, a month or even sooner.

We obtained some insight into this problem while investigating the identity of the end product in the urine of parenterally injected hyaluronidase. It is known that the subcutaneous administration of hyaluronidase produces depolymerization of hyaluronic acid. How such depolymerization affects the surface tension of urine secreted by the kidneys at a distance was rather perplexing. Certainly large molecules of hyaluronic acid (M. W. approximately 500,000) would not pass the glomerular wall (capillary), and there is ample evidence that hyaluronidase is rapidly inactivated by the proteins of the blood stream. We, therefore, postulated that only highly depolymerized fractions of hyaluronic acid could enter the circulation and reach the glomerular filtrate in appreciable concentration. One of the end products of depolymerization of hyaluronic acid is glucuronic acid and this is available in the pure state as a synthetic chemical substance

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Read at annual meeting, American Urological Association, New York, N. Y., May 31, 1954.

marketed as glucuronolactone.* It was decided to study the effects of this substance on the surface tension of the urine of patients known to have formed renal calculi; it appeared reasonable to evaluate the effects of one of the end products of depolymerization of hyaluronic acid in view of the previously demonstrated effect of the subcutaneous administration of hyaluronidase.

In order to obtain a control group for determination of the surface tension levels in the urine of a normal individual, 1200 samples of urine from 100 nonpregnant patients who gave no history of gallbladder disease, liver disease or urinary calculus disease were examined. The results were as follows:

Surface Tension in Dynes/cm.	Number of Urine Specimens	Per cent of Total
63–65	144	12
66–68	872	72.7
69–71	160	13.3
72–73	24	2

The urinary surface tension levels of 25 patients with history of renal calculi disclosed the following:

Surface Tension in Dynes/cm.	Number of Urine Specimens	Per cent of Total
63–65	40	8
66–68	110	22
69–71	230	46
72–73	120	24

Glucuronolactone was given orally 4 times a day to the 25 stone-forming patients and serial specimens of the urine were examined. The effects were as follows:

1) Eight patients who originally had surface tension values ranging between 66 dynes/cm. and 69 dynes/cm. showed no significant changes in these determinations.

2) One patient whose base-line determinations averaged 69.5 dynes/cm. responded to medication by a persistent elevation to 72 dynes/cm.

3) Three patients whose surface tensions ranged between 69 dynes/cm. and 71 dynes/cm. developed an initial fall in surface tension but returned to essentially the level recorded before medication.

4) Two patients in the 69 dynes/cm. to 71 dynes/cm. group had a persistent fall of 1.5 dynes/cm. to 2 dynes/cm.

5) Eleven patients whose base-line determinations were in the 70 dynes/cm. to 73 dynes/cm. range responded by maintaining surface tension levels within the 66 dynes/cm. to 69 dynes/cm. grouping, some of the determinations being recorded at 62 dynes/cm.

It is evident from these above determinations that we are able to lower the surface tension values of urine to a normal range in a large percentage of cases by the oral administration of glucuronolactone. The medication has its greatest effect in those instances in which the urinary surface tension levels were initially persistently elevated (70 dynes/cm. to 73 dynes/cm.). It would therefore seem probable that the beneficial effects attributed to the subcutaneous injection of hyaluronidase result from the presence of glucuronic acid in the urine, causing colloidal changes with ensuing alterations in urinary surface tension.

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* Glucuronolactone supplied for this investigation by the Corn Products Refining Co., N. Y.

The significance of these findings is manifest. Generally speaking, unless there is a marked excess in the crystalloid element of the urine, our findings indicate that active stone formation does not take place in the presence of urine having normal surface tension levels (sustained 66 dynes/cm. to 69 dynes/cm.). Hence, the administration of glucuronolactone would not seem indicated in these instances. When the urinary surface tension has been within normal range (66 dynes/cm. to 69 dynes/cm.) we have not been able to materially lower it with the present dosage of glucuronolactone. When, however, there is a sustained elevation (70 dynes/cm. to 73 dynes/cm.) every effort should be made to effect a reduction. We feel that, at present, the agent of choice to accomplish this is glucuronolactone. While hyaluronidase may have a similar effect in selected instances, this substance tends to lose its effectiveness over a period of time because of the formation of antihyaluronidase.

We wish to emphasize that we do not advocate the administration of this product (glucuronolactone) to *all* patients in an effort to further lower the incidence of recurrent renal calculi. Rather each individual must be carefully studied for his special needs. An exacting plan must be formulated whereby the fluid intake, vitamin needs, urinary pH regulation and dietary management meet the particular requirements. In addition frequent determinations should be made of the surface tension levels of the urine. Occasional fluctuations are not considered significant but when a sustained elevation (70 dynes/cm. to 73 dynes/cm.) becomes manifest glucuronolactone should be given. Thereafter, at varying intervals the medication should be discontinued and resultant surface tension levels observed. As long as normal levels (65–69 dynes/cm.) are maintained no further glucuronolactone is indicated, but its use should be resumed if a sustained elevation recurs. This plan is in accordance with the idea that the factors (aside from obstruction and infection) concerned with calculus formation are not constant in an individual but rather inconstant and vacillating. Aside from crystalloid concentration in the urine, the surface tension value of the urine appears to be a readily accessible index of these changes. Our patients are instructed in the use of the urotensiometer (Revici) so that they are able to record their own urinary surface tension values twice daily. This daily record makes any significant change apparent. The evaluation of the effectiveness of this regimen can only be made after follow-up of these and other patients over a protracted period.

Before concluding, it might be well to note that the lowest urinary surface tension values we have encountered (55 dynes/cm.) have been in pregnant patients and in jaundiced patients. Low readings have been encountered also in

Addison's disease. Certain infections tend to lower while others tend to elevate surface tension. Stress, ACTH or cortisone administration and Cushing's syndrome are associated with urines of high surface tension. The significance of these changes is not fully understood but a knowledge of their causes may well hold many of the answers of calculus formation.

SUMMARY AND CONCLUSIONS

Our findings indicate that, unless there is a marked excess in the crystalloid element of the urine, active stone formation does not take place in urine having normal surface tension values.

Patients with a past or present history of urinary calculi generally have higher urinary surface tension levels than patients without this history.

When urinary surface tension levels have been elevated we have been able to bring these values down to normal levels in a high percentage of cases by oral administration of glucuronolactone.

In the prophylaxis of urinary calculi an exacting plan must be formulated whereby the fluid intake, vitamin needs, urinary pH regulation and dietary management meet the individual needs. In addition the patient is instructed in the use of the Revici urotensiometer so that he is capable of recording urinary surface tension levels twice daily. Since these levels appear to be an index of the inconstant and vacillating factors (aside from obstruction, infection) associated with calculus formation, significant changes may be managed accordingly.

We feel that, at present, the agent of choice to lower urinary surface tension from elevated levels is glucuronolactone.

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STUDY OF THE URINARY SURFACE TENSION AND PROTECTIVE COLLOIDS IN UROLITHIASIS; USE OF THE REVICI UROTENSIOMETER

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Several years ago, we made a preliminary clinical study of the surface tension of urine in a large number of urological cases. The surface tension values of the urine of all patients seen in an active urological office were routinely determined by utilizing a simple glass capillary pipette with a scale that permitted direct readings in dynes per centimeter. Our experience with this urotensiometer designed by Revici[1] indicated that the surface tension of urine could be determined accurately in a matter of a few seconds by means of an inexpensive instrument that was as easy to use as the ordinary clinical thermometer.

In the light of recent developments in studies on the fundamental mechanisms involved in renal stone production, the availability of a simple device that can be used to determine the surface tension of urine is a matter of wide interest. The applicability of this particular test to the field of Urology was suggested by the work of Butt, Hauser and Seifter. Since 1950, these authors have published a series of articles[2-10] emphasizing the role of protective urinary colloids in the treatment and prevention of renal lithiasis. They have suggested that the urinary colloids prevent the precipitation and agglomeration of the crystalloid elements which exist in the urine in concentrations far exceeding their solubility in water. Their studies of this protective role of the colloids have opened up a new and potentially important medical approach to the prevention and treatment of urinary calculi.

Butt's experiences in the South Pacific during World War II, and in West Florida, which is an endemic stone area, indicated that colloid particles observed

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[10] Butt, A. J., Hauser, E. A. and Seifter, J.: Effect of hyaluronidase on urine and its possible significance in renal lithiasis. J. A. M. A., 150: 1096, 1952.

in urine by means of the ultramicroscope were somehow related to the phenomenon of stone formation.[2, 3] He found that the number of colloid particles was higher in the urine of Negroes than of whites, higher in the urine of women than of men, and also was increased during pregnancy. These findings seemed to correlate with the knowledge that calculus disease is relatively rare among Negroes,[11, 12] is less common among females than males[7, 8] and is very rare in pregnant women,[13-16] in spite of the stasis and inflammation that are common in pregnancy.

Hauser has investigated the problem by means of various refined techniques employed by colloid chemists. These include studies of the surface tension of the urine, utilizing the pendant drop method,[17] determination of the electrical charge of the colloid particles by electrophoresis, and examination of the evaporated urine smear by means of the "Ultropak" microscope.[4, 5] These studies have indicated that surface active hydrophilic colloids may prevent the growth and agglomeration of inorganic crystalline material which might otherwise precipitate from the supersaturated state to form calculi in the urinary tract.

Butt and his associates[2, 7-10] have reported on the treatment of recurrent stone formers with repeated injections of hyaluronidase. Their results indicate that the treatment is effective in raising the level of colloid activity and in preventing stone formation. Seifter suggested that the subcutaneous administration of the enzyme hyaluronidase acted upon the collagen substrate to release hyaluronates or hyaluronic acid in increased quantities in the urine.[10] The hyaluronate forms colloidal micelles which act as a dispersing agent in the urine, inhibiting the new formation or further growth of stones.

The theory that an imbalance between colloid and crystalloid components of the urine plays an important role in stone formation, first suggested by Ebstein in 1884,[18] is certainly an intriguing one that deserves and is receiving serious consideration and study, particularly by urologists. The techniques that have been employed by Butt, Hauser and Seifter to investigate the problem and to establish effective dosage schedules for the treatment of calculus disease are highly complex and cumbersome, and are not well adapted for routine clinical use. Progress along this line is seriously limited because of the lack of a suitable method of determining the effects of various therapeutic procedures upon the urinary colloids.

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[17] Andreas, J. M., Hauser, E. A. and Tucker, W. R.: Boundary tension by pendant drops. J. Phys. Chem., 42: 1001, 1938.

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The possibility that the Revici urotensiometer might facilitate studies of the role of protective colloids in the prevention and treatment of renal lithiasis led one of us (R. A. R.) to study the relationship between the surface tension of urine, as determined by this instrument, with the number of colloids observed per field by means of the ultramicroscope.[19] A close, although not a precise quantitative relationship was found to exist. Urine having a high concentration of colloids had low surface tension, and urines with a low concentration of colloids generally had a high surface tension.

To the colloid chemist,[20] two of the most important basic physical effects of surface active agents are: 1) their effect in sharply lowering the surface tension, and 2) their solubilizing effect upon normally insoluble substances. The former effect is related to the strong interface adsorption of individual surface acting ions or molecules, while the latter effect depends upon the presence of colloidal micelles formed by the spontaneous association of the surface active ions or molecules. The micelles exist in thermodynamically stable equilibrium with the simple ions or molecules. Most authors agree that the pure surface effects are due to the unassociated ions or molecules, and that any factor which affects micelle formation in the bulk will also affect the availability of molecules or ions for surface film formation. Very possibly, the colloidal particles or micelles visualized under the ultramicroscope begin to form in large amounts only when a definite, relatively narrow concentration range is reached.

The surface tension and solubilizing effects of colloidal micelles are closely related, although the correlation is not a simple quantitative one. Consequently the surface tension can be utilized as a means of determining the relative concentration of protective colloids within the urine. The surface tension will be low when the concentration of colloids and of the unassociated surface active ions or molecules is high. Conversely, the surface tension will be high when the concentration of colloidal micelles and of the surface active ions or molecules is low.

Several different methods exist for the determination of surface tension. Most of them involve the use of intricate instruments and techniques and the solution of involved formulae. In the dynamic methods, the time factor seriously influences the determinations. Thus they are not well adapted for measuring the surface tension of highly complex physiological solutions like urine, in which the different molecules redistribute themselves between the surface and bulk of the solution at varying rates. Relatively static methods such as the capillary method, largely obviate this difficulty. The capillary method which is the simplest, appears to be the most useful and accurate for purposes of clinical analyses.

The urotensiometer designed by Revici[1] consists of a straight glass capillary tube, measuring approximately 150 mm. in length. The outside diameter of the tube is 5–6 mm. and the bore diameter is approximately 0.5 mm. The tube is calibrated to permit direct reading in dynes/cm. of the surface tension of a liquid having a specific gravity of 1.015 (corresponding to the average specific gravity of urine). The maximum error for urines with specific gravities covering the clinically observed range (1.002 – 1.032) is ±1 dyne/cm.

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[19] Ravich, R. A.: Relationship of colloids to the surface tension of urine. Science, 117: 561, 1953.

[20] Schwartz, A. M. and Perry, J. W.: Surface Active Agents. Their Chemistry and Technology. New York: Interscience, 1949.

In order to determine the surface tension of a urine specimen, the tip of the Revici urotensiometer is introduced into the bulk of the specimen and a column of urine, uninterrupted by air bubbles, is drawn up to the top line of the scale by gentle mouth suction. The tip of the tube is withdrawn from the specimen and the fall of the column of urine is observed in the vertically held tube. The first point at which the fall of the top of the column stops or the rate of descent is distinctly slowed is read as the surface tension of the specimen. This point (P_1) is reached within less than five seconds. Thereafter, the column will resume its descent, reaching a second point (P_2), at which it is interrupted or slowed after 30–40 seconds. The column will resume its fall and will finally reach a final point of equilibrium (P_3), after about 15–20 minutes. For routine purposes, we have considered the first point (P_1) as representing the surface tension of a specimen. Readings are made directly from the scale in dynes/cm. without any calculations being required.

The series herein presented includes data on afternoon urine specimens from 519 white patients, of whom 330 were males and 189 females. All the female urines were catheterized specimens. These have been divided into seven separate groups for purposes of comparison of the data:

Group I: Patients with *calculus disease* of kidney or ureter existing at the time of the urine examination;

Group II: Patients with a *history of calculus disease* prior to the examination of the urine, but free of evidence of calculus at the time of the study;

Group III: Patients with roentgenographic and cystoscopic evidence of urostasis due to obstruction but without existing or prior calculus disease;

Group IV: Patients with active *inflammation* of the urinary tract, e.g. pyelitis, pyelonephritis, cystitis, trigonitis;

Group V: A *miscellaneous* group of patients, many of whom had vague symptomatology without any objective evidence of organic disease involving the urinary tract;

Group VI: Patients with benign or malignant *neoplasms* in some part of the urinary tract;

Group VII: Male patients with *prostatism*.

The total number of cases and the number of males and females included in each group are shown in table 1.

The surface tension values found varied between 73 and 56 dynes/cm. The average surface tension for the entire series was 67 dynes/cm. Average values for the two sexes differed somewhat, being higher in all groups among females.

The average surface tension values were highest for the groups with existing calculus disease and urostasis. Those with a past history of calculus, and with

TABLE 1

Group	Condition	Number of Cases	Males	Females	Average Surface Tension Dynes/Cm.
I	Calculus	59	42	17	68
II	History of calculus	94	45	49	67
III	Urostasis	57	23	34	68
IV	Inflammation	47	11	36	67
V	Miscellaneous	122	82	40	66
VI	Neoplasm	38	25	13	66
VII	Prostatism	102	102	—	66
Total		519	330	189	67

inflammation had average values that were slightly lower. Average surface tension values were lowest in the control miscellaneous group with nonurological conditions, those with neoplasms of the urinary tract, and with prostatic disease (table 1). These findings appear to confirm those of Butt, Hauser and Seifter, who found decreased colloidal concentrations and higher surface tension values in individuals with calculus disease, and among groups having a relatively greater susceptibility to stone formation.

There are a great many controllable and uncontrollable factors which may influence surface tension values. Diet and fluid intake do not seem to influence it, whereas changes do appear to be related to the time of day. The surface tension changes in the hourly urine specimens of a healthy thirty year old man on a standard hourly intake of food and liquid show a wave-like rise and fall in surface tension values, with the highest values between 1–7 a.m. and the lowest between 3–9 p.m. The present studies were based on urine specimens voided between 1 and 5 p.m., and are therefore somewhat lower than would be found using morning specimens.

Various disease conditions influence the surface tension. The normal individual shows a relative lability in his excretion of surface active substances in the urine, with values tending to fluctuate over ranges of 6–8 dynes/cm. at various times during the day and on successive days, as measured by the urotensiometer. Various abnormal metabolic, hormonal or disease conditions tend to reduce this lability of excretion of surface active agents. In chronic diseases such

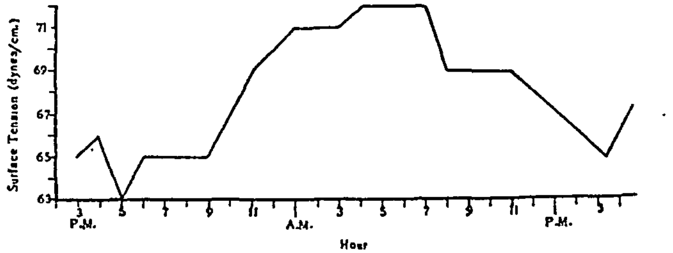

FIG. 1. Changes in surface tension of hourly urine specimens in a healthy 30 year old man on standard hourly intake of food and water.

as cancer,[21] tuberculosis[22] and schizophrenia,[23] high or low surface tension values may be maintained in a narrow range over long periods of time, a finding which has been termed "isostalacturia"[24]

It is of interest to note that the group with urostasis showed average surface tension values approximating those found among patients with calculus disease. The possibility exists that the observed reduction in surface active agents indicated by the high surface tension values in cases with urostasis accounts for the relationship of urostasis to stone formation recognized almost thirty years ago by one of us (A. R.).[25, 26]

Butt, Seifter and Hauser, noting as we have that surface active or protective colloids are reduced in the presence of urinary infection, have related this to the action of bacterial hyaluronidase upon the hyaluronate in the urine. Whereas testicular hyaluronidase depolymerizes hyaluronate, bacterial hyaluronidase causes degradation of the hyaluronate present in the urine thereby removing protective colloid, raising the surface tension and so enhancing the possibility of stone formation.[27]

We are currently studying the influence of various agents upon the excretion of surface active substances in the urine, as indicated by serial surface tension analyses using the Revici urotensiometer. This simple laboratory device can greatly facilitate studies of the role of surface active, protective, dispersing and solubilizing colloids in the prevention and treatment of renal lithiasis. It can be of use in guiding the therapy of individual patients in whom it is desirable to maintain a high level of excretion of surface active substances in the urine in order to reduce the tendency to stone formation.

SUMMARY AND CONCLUSIONS

The work of Butt, Hauser and Seifter has focused attention upon the role of surface active colloids in inhibiting the precipitation and agglomeration of inorganic matter in the urine, and preventing the formation of renal lithiasis. Studies concerning this intriguing new approach to the problem of stone formation are limited by the complexities of available methods for determination of urinary colloids and the surface tension of the urine.

The urotensiometer designed by Revici provides a simple, inexpensive instrument capable of giving accurate surface tension values for a complex physiological solution like urine within a few seconds. Readings are made directly in dynes/cm. and surface tension determinations can therefore be a routine laboratory or office procedure. The method is no more difficult than reading a clinical thermometer, and can be carried out by lay people after a few minutes of instruction.

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Studies have shown that average surface tension values were higher among patients with calculus disease and urostasis than among those with other urological conditions and a miscellaneous group of cases with various nonurological complaints. The findings suggest that the Revici urotensiometer can be useful in guiding therapeutic measures aimed at maintaining a high level of excretion of surface active substances in the urine in patients in whom it is necessary to reduce the tendency to stone formation.

We are indebted to Emanuel Revici, M.D. for permission to use the experimental model of the urotensiometer, and to Mr. Emil Davidson of Clay-Adams Co. for technical advice.

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LOW PROTEIN DIET IN THE MANAGEMENT OF RECURRENT URIC ACID STONES

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Concretions of uric acid amount to about six per cent of urinary tract stones.[1] Management in these cases includes alkalinization of the urine, great fluid intake and a low purine diet. These measures are aimed at enhancing the relative solubility of uric acid in the urine and limiting the total quantity which must be excreted. This treatment often is not successful in preventing recurrences of stones.

The recognized antecedents of urinary uric acid are the purines.[2, 3] Uric acid excretion rises and falls concomitantly with the increase and decrease of purines in an otherwise normal and controlled diet. Recent metabolic studies utilizing isotope tracer techniques demonstrate a considerable endogenous synthesis of purines from a variety of ingested nitrogen compounds. These endogenous purines give rise to uric acid. Unlike other mammals which oxidize uric acid to allantoin, man must eliminate uric acid in the urine. It seemed to us that a further diminution of uric acid in the urine might occur if the total nitrogenous intake were restricted than if purines alone were withheld. If this was so, a low protein diet rather than a low purine diet would be indicated in patients with stones.

METHODS

The subjects for this study were 10 patients with histories of multiple episodes of urate stones. All were male. They ranged in age from 37 to 70 years. Seven subjects had gouty arthritis. Kidney function was good in all patients but one, G. S. One patient, M. Gd., was given probenecid for 1 week during the course of dietary restriction, and received phenylbutazone during the off diet study period. After baseline determinations of serum uric acid, urinary uric acid concentration, 24 hour uric acid excretion and urine pH were obtained, the subjects were placed on a diet containing only 30–40 gm. high quality protein but adequate in calories to maintain weight. Four subjects had been on a low-purine diet at the time of the baseline studies. The chemical determinations were repeated at intervals during the study period and at its conclusion. Creatinine determinations were performed on the 24 hour urines to check the adequacy of collection. The period of protein restriction ranged from 3 weeks to 7 months. One case was allowed a period of ordinary diet and then placed on protein restriction again. Another case was followed after cessation of protein restriction.

Accepted for publication May 21, 1954.

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[3] Christman, A. A.: Purine and pyrimidine metabolism. Physiol. Rev., 32: 303, 1952.

TABLE 1

Subj.	Age		Serum, Uric Acid	Urine		
				pH	Concentr. uric acid	24 hour uric acid
			mg. per cent		*mg. per cent*	*mg.*
J. B.	47	Baseline*	8.6	5.5	76	1,277
		On diet 3 wks.		7.0	54	777
T. B.	42	Baseline*	6.9	5.0	69	666
		On diet 3 wks.		5.9	14	365
H. G.	37	Baseline*	7.3	7.5	64	874
		On diet 7 mos.	6.0	7.0	27	542
		Off diet 2 mos.	5.9	7.0	34	723
		On diet 7 mos.	6.1	7.3	16	415
M. Gd.	46	Baseline*	9.4	5.5	55	880
		On diet 3 mos.	7.6	6.5	35	700
		Off diet 1 mo.	7.2	5.7	44	1,180
M. Gr.	43	Baseline	6.1	5.0	34	584
		On diet 4 mos.	5.4	5.5	31	446
J. M.	44	Baseline	5.8	5.5	62	779
		On diet 2 mos.	5.0	6.0	22	538
C. N.	70	Baseline	7.4	6.5	55	811
		On diet 4 mos.		6.5	38	656
G. S.	51	Baseline	8.8	6.0	26	198
		On diet 5 wks.		6.0	30	154
N. T.	53	Baseline	7.2	5.5	80	944
		On diet 3 mos.	5.8	6.0	21	410
F. W.	58	Baseline	7.3	5.2	45	734
		On diet 2 mos.	4.9	6.8	23	536

* On low purine diet at time of baseline studies.

Uric acid was determined by an adaptation of the Brown modification of the Folin method.[4] The Jaffe reaction was used to determine creatinine.[5]

RESULTS

The results of the study are summarized in table 1. The average baseline uric acid excretion of our subjects was 775 mg./24 hours as compared with values of 300 to 500 mg./24 hours in normal adults.[6] Seven of the 10 subjects had a concentration of uric acid in the urine greater than 50 mg. per cent in contrast to one of 12 nongouty subjects studied by Talbott.[7] After protein restriction the average uric acid excretion was 512 mg./24 hours, an average decrease of 263 mg./24 hours. The concentration of urinary uric acid fell an average of 29.3 mg. per cent and all but one subject now excreted less than 50 mg. per cent. Eight of 10 subjects were found to have an elevated blood uric acid (normal limit = 6.3 mg. per cent).

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[5] Bonsnes, R. W. and Taussky, H. H.: On the colorimetric determination of creatinine by the Jaffe reaction. J. Biol. Chem., 158: 581, 1945.

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After the period of protein restriction, two subjects were permitted a demand diet (no protein restriction). The level of uric acid excretion became elevated. A depression was again observed in one subject who returned to protein restriction.

There were recurrences of uric acid stones in 2 cases, H. G. and M. Gd., during the study period. In the first case this occurred during the period of demand diet, and in the second case after one week of treatment with probenecid.

DISCUSSION

The composition of the diet is a determinant of the magnitude of purine formation and the excretion of the metabolic end product, uric acid. Protein foods contribute to urate production in part by their content of preformed purines but more significantly by providing nitrogen sources for the synthesis of purines within the organism. In our cases, a highly significant decline in urate excretion has occurred on dietary protein restriction. This diminution in urate excretion occurred in four patients who had already been on a purine restricted diet at the inception of the study. These results are in agreement with the findings of a 200 to 300 mg./24 hour decline in urate excretion on protein restriction by Gutman and Yu[8] in gouty patients. While a diet containing one gram protein per kilogram body weight is optimal for growth, development and general well-being, a diet containing 0.2 gram high quality protein per kilogram body weight will not result in a nutritional deficiency of protein.[9]

Eight of 10 cases had an elevated serum uric acid level and all subjects except the one with marked renal impairment eliminated an abnormally large amount of uric acid in the urine at the start of the study. A determination of 24 hour urinary uric acid may be of diagnostic help when uric acid stone is suspected.

The administration of uricosuric agents such as probenecid results in an increase of urate excretion in the urine.[10] Not infrequently urate stones are precipitated at the start of such courses of treatment. This happened in one of our patients. Restriction of protein prior to treatment with uricosuric agents may lessen the likelihood of stone formation.

Prophylactic management in cases of uric acid stones is complex and not entirely successful.[11, 12] The usefulness of alkalinizing the urine and increasing fluid intake is well recognized. The salts of uric acid which are formed in alkaline urine are more soluble than the free acid and tend to remain in supersaturated solution.[13] However, the common alkalinizing agents do not maintain a consistently alkaline urine over all 24 hours. Whereas the overall fluid intake may be large there still may be periods when the hourly urine volume is so small that the solubility of uric acid is exceeded. These considerations may help explain failures. A low protein diet employed as an adjunct to alkalinization and hydration should result in improved management of patients suffering from uric acid stones.

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[8] Gutman, A. B. and Yu, T. F.: Current principles of management in gout. Am. J. Med., **13:** 744, 1952.

[9] Sahyun, E. M.. Proteins and Amino Acids in Nutrition. New York: Reinhold Publishing Co., 1948.

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SUMMARY

A diet low in protein resulted in a significant decrease in urinary urate excretion in ten patients who had recurrent uric acid stones. Elevation of serum uric acid in eight patients and of urinary uric acid levels in nine patients was found before dietary restriction. A low protein diet providing 30–40 grams of protein daily is recommended as an adjunct to alkalinization and hydration in management of uric acid stones.

We are indebted to the staff of the chemistry division, William Pepper Laboratory of Clinical Medicine, for assistance with the chemical determinations.

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THE VENOUS JUNCTION OF THE GLOMERULAR ARTERY

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In 1951 we described a glomerular anatomy different to the one which was known up until then.

The moulds made with latex permitted the dissection of the glomerulus much more easily than with any other filling substance, and from that study we drew the following conclusions. The renal glomerulus is not really a capillary network interposed between two arterial vessels, but it is only a bent arterial vessel having, in its external angle, several evaginations of different shapes and sizes, keeping therefore the integrity of the arterial vessel throughout its whole extension. This conception, to our belief, greatly favors the interpretation of the renal physiology and of many a pathological state too, that would be very difficult to explain through the ancient concepts of glomerular constitution (fig. 1).

In this work, we are interested to show the anatomic constitution of the arterial portion that goes from the glomerulus to the drainage veins. It might seem unimportant to devote our attention to so small a portion of the renal arterial system, but we are convinced that such a portion is, perhaps, the most important renal sanguineous part from the physiological urinary point of view. We also believe that the alterations in this part of the renal circulatory system may produce pathological modifications of vital importance in the effective yielding of the organ.

In the conclusions drawn from our later work, we have also seen that the blood may, under certain circumstances, flow freely along the artery, without passing through the glomerular loops, but though we can, with such concept, explain the deviation of the sanguineous flood, with no need of passing through the glomerulus, we still meet the difficulty of explaining the flowing of the blood into the vein and its restitution to the general flood.

We could address ourselves to the "shunt" of Trueta and colleagues, but we would not understand its functioning clearly, especially because an exclusively juxtamedullar deviation would greatly embarrass the renal parenchyma. The periods of rest of the parenchyma occur very frequently, not to say constantly, throughout the course of the renal function, such as those of circulation without momentary production of urine, though in a segmentary form. Besides the renal parenchyma cannot be deprived of circulation for a long period, without threatening its integrity, and though the juxtamedullar "shunt" of Trueta might mean a situation of extreme emergency, it cannot be considered as habitual in the kidney.

If we base our opinion on the idea that each artery forms a glomerulus in its latest end and that these arteries form a capillary bed before its venous junction, the hematic unbalanced condition of the kidney would surely endanger

Read at annual meeting, American Urological Association, St. Louis, Mo., May 11, 1953.

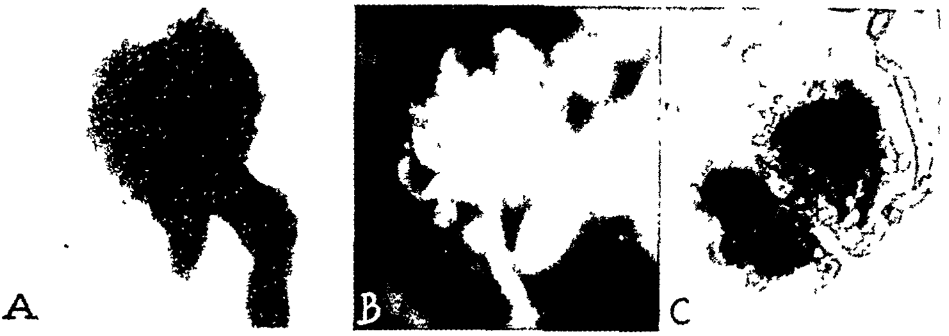

FIG. 1. *A*, Latex mould of normal glomerulus with poor digestion of organic tissue. *B*, normal glomerulus where digestion has been properly performed. Arterial unity and glomerular evaginations may be clearly seen. *C*, transparent latex mould of normal glomerulus where arterial unity is perfectly clear.

the integrity of the organ, except that the venous junction of the glomerular artery had anatomical dispositions that would help the sudden circulatory alterations.

Before these facts, we made up our minds to start the study of the arteries and of the veins, by means of latex moulds, with the following technique.

TECHNIQUE

We have not fundamentally modified the technique of the injection of the vascular tree of the kidney, described in former works. Nevertheless, some details should be added in order to study simultaneously arteries and veins.

To begin with, we go on working obtaining anatomical pieces within the two hours after death. During the necrospy process, we do not only remove the kidney, but we also extirpate the perirenal fat, that is to say, that the enucleation is done by the outside of the Zuckerkandl's fascia. This modification is exclusively due to the necessity of having an organ with a sound venous system, that is to say, without the risk of injuries, which are irreparable due to the fragility of the venous wall whose tears, always longitudinal, cannot be satisfactorily sutured.

Having obtained the piece, we proceed to its washing with physiological serum, at a pressure up to 12 to 15 cm. of water, and during this washing we rid the kidney of its perirenal fat, tying up all the venous and arterial vessels that must be sectioned.

When the washing has been done and we have obtained clear liquid through the vein, it is convenient, in spite of all the cares that we have taken in obtaining the organ, to try the integrity of the venous tree, injecting physiological serum through the renal vein at an exact and uniform pressure up to 2 to 4 cm. of mercury, with the only object of avoiding losses of latex.

Now we have the kidney with its arteriovenous tree full of physiological serum. Therefore, it is absolutely necessary to empty it, forcing a current of air to pass for a few minutes from the artery to the vein.

When the renal circulatory system is empty and all the losses have been controlled, we proceed to inject an ammoniacal solution of latex commerically pure, that is to say at 65 per cent, which we dilute in a proportion of from 1 to 4 in pure ammonia, with the object of obtaining an easy flowing liquid. Besides, as we inject two different vascular systems, the arterial and the venous, we must use differently colored latex, continuing with white latex for the arterial tree and with black latex for the venous tree This black latex is obtained adding India ink in sufficient quantity.

All the elements being ready, we first proceed to inject the venous system at a pressure up to 2 to 4 cm of mercury, which is equivalent to the pressure of the inferior vena cava, in horizontal decubitus Thus we observe the filling of the renal veins and the formation of the Verhayen stars and, immediately, the swelling of the kidney, that shows us the total filling of the venous tree This is done, according to the size of the piece, with 100 to 150 cc of solution. We have never observed the slightest trace of reflux of black latex up through the artery, not even increasing the pressure to obtain the rupture of the renal vein. When the black filling has been done, and without modifying the pressure of the venous injection, we introduce the white latex at a pressure that depends on the habitual arterial pressure of the patient, thus observing the subcapsular circulation.

The filling of the whole renal circulatory tree has been thus completed. We place the piece in a solution of formaldehyde at 5 per cent until its microscopic study, which is preceded by methodic corrosion by means of pure hydrochloric acid.

RESULTS

The anatomical structure of the glomerular artery, between the glomerulus and the vein, can be shown in two well defined forms, forms which at the same time may undergo a series of changes, but that, in short, we can divide in two great groups.

The first group is formed by those vessels that undergo the habitual division into small capillaries before joining the venous trunk.

The second group is constituted by those vessels that end directly in a vein, without obvious interposition of a prevenous capillary system.

First group We shall first describe the different varieties we have met in this group and, at the end of the chapter, we shall study in detail their passing into the vein

We shall classify these varieties in different subgroups. Up to now, we have found four, which we believe to be characteristic In subgroup a, we enclose those glomerular arteries, which immediately divide into capillaries, in subgroup b, we group all these arteries that give off capillaries after the artery has divided into two or more arterioles, in subgroup c, we place all those glomerular arteries that give off capillaries at a distance, and in the subgroup d, we enclose all those vessels that also have venous capillaries before joining the vein

There are, of course, different intermediate stages Nevertheless, we shall supply further details of this morphology.

Subgroup a It should be remarked that this one is the most numerous group

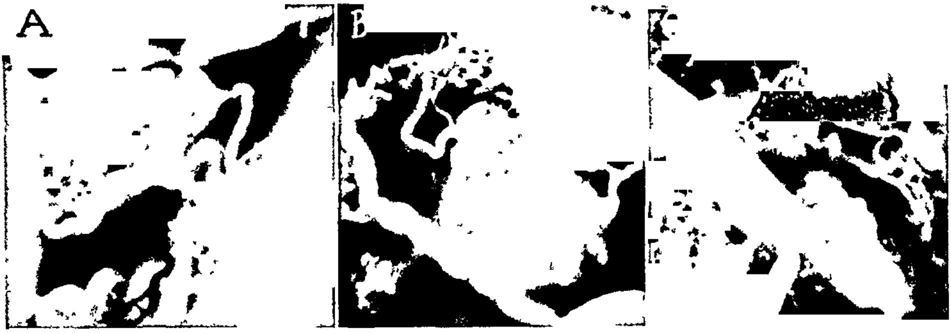

FIG. 2. This type of postglomerular portion of artery belongs to group I, subgroup a, in which capillary division system is formed immediately after glomerulus.

Generally when the kidney is observed slightly magnified, if the organic substance has been well digested and there only remain the white and black latex that represent arteries and veins respectively, the glomerular arteries are seen spreading all over the kidney forming numberless tiny capillary networks. Each of these networks depends on a glomerular artery. We shall see how their formation takes place: when the glomerular artery has formed the glomerulus, it continues and practically at once divides in several small arterioles that apparently form a reticule of a size larger in several diameters than that of the glomerulus of the artery upon which it depends.

This capillary network is particularly interesting. It does not split, so to say, dichotomically, but it seems to give off several branches, that form a whole of a network appearance. But if we make a dissection a little more carefully, we shall be surprised to observe that, generally, those network-like branches are not anastomosed and the pseudo-meshes of the net are formed by the superposition or intercrossing of the same capillary branches (fig. 2).

Subgroup b. In this subgroup we place the glomerular arteries that, instead of spreading in a network that will precede its joining to the vein, split in two or more arterioles that will independently form a capillary network each. The careful dissection of these capillary networks shows us that they are never joined among them, but that they are intercrossed and that they will always join to veins and never to neighboring capillaries (fig. 3).

Thus we verify once more that the capillary of the kidney is independent

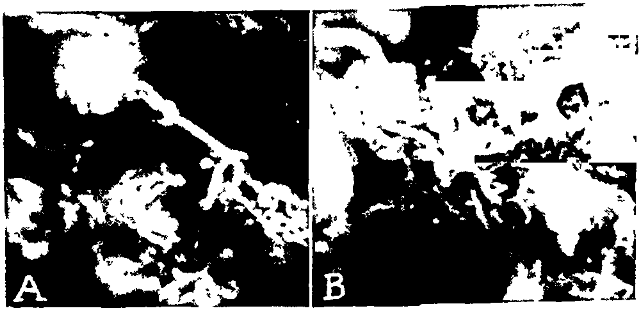

FIG. 3. Artery belonging to group I, subgroup b. Postglomerular part of artery divides into several branches before forming capillaries.

and has no anastomotic net; but what draws our attention is that there are no junctions of any kind, even among the capillaries that proceed from the arterioles of the same trunk.

The arteries of this subgroup might have two, three or more divisions. Sometimes we can follow these divisions right up to the vein, but other times, the structure becomes so fragile that they rupture and they do not fill properly with latex.

Subgroup c. In this subgroup we observe that the postglomerular portion of the artery, instead of being short, is very long, disproportionately long in relation to those we have seen in the former subgroups. These arteries form their capillaries at a distance of 6, 7 or more diameters of glomerulus. Sometimes this artery, thus elongated, forms such as the others, a capillary net. Others it divides in two or three branches such as subgroup b, but also forming capillaries which are independent one from the others (fig. 4).

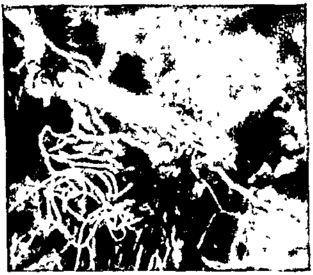

FIG. 4. Artery belonging to group I, subgroup c. Note long postglomerular portion of artery before its division.

To these subgroups we must add the subgroup d, in which the capillary endings are similar to the previous ones but where it is evident that the venous capillaries continue before opening into the vein.

Venous junction of the glomerular arteries belonging to group I: The varieties of group I have a common character that is the division of the glomerular arteries into thin capillaries before their junction to the vein. We shall describe the arteriovenous junction as a whole since most of the capillaries open directly into a stout vein.

The interposition of a venous capillary net may exist, subgroup d, but we are not very sure if it is not something false, on account of an excessive pressure when injecting the latex along the stout renal vein.

Observing the renal venous system we shall be surprised to see how poor it is in small vessels; it would seem constituted only by great trunks as if it were a pruned tree that, deprived of its boughs and foliage, is left with its thick branches only. But this image, which appears when the latex is injected through the vein only, is fully seen when the artery is also injected. This arteriovenous whole takes immediately another aspect and we can then observe how numberless

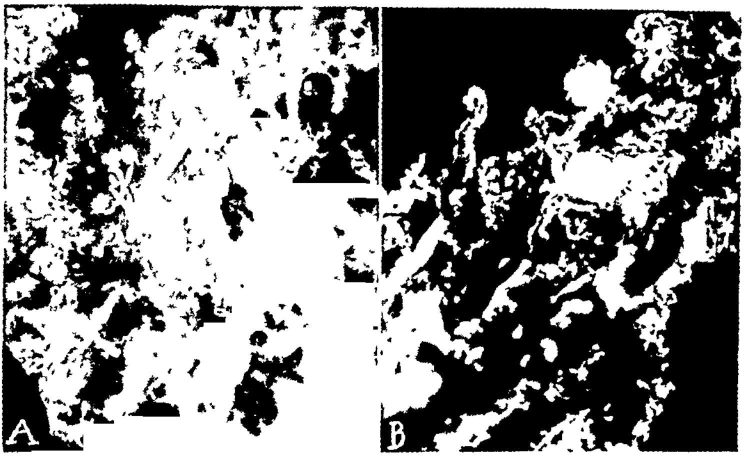

FIG. 5. *A*, panoramic view of arteriovenous junctions. *B*, photomicrograph of arteriovenous junctions.

arteriolary vessels gather around the extremities of those thick venous trunks. These vessels whirl and press around their joining point forming the arteriovenous junction.

Observing thoroughly a complete preparation (fig. 5, *A*) we see, with slight magnification, that the stout venous trunks are specially surrounded by arterial and arteriovenous capillaries, while the thick arteries remain free. In figure 5, *B*, we can see the glomeruli greatly magnified. Their glomerular arteries give off compact branches of capillaries which are in close contact with the veins, so much so, that we can hardly see, now and then, a free venous wall.

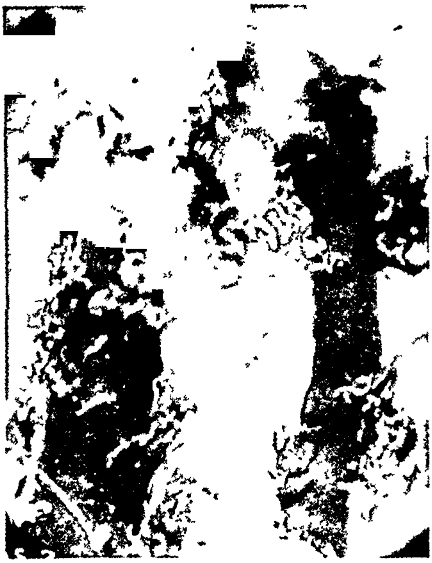

FIG. 6

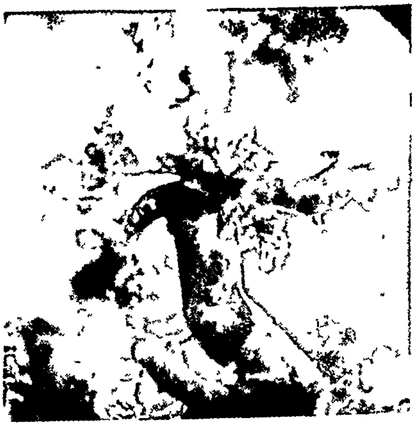

FIG. 7

FIG. 6. Two stout venous vessels receive directly numberless capillaries, that sometimes gather in a vein of less caliber before joining major vein

FIG. 7. Lacunar disposition of arterial capillaries before joining vein

If we dissect these veins (fig. 6), ridding them from all the elements that surround them, with the object of seeing them, so to say, naked, we can observe how the thin capillaries open into the stout venous trunks.

There are different forms of junctions. The most common one can be seen in the same figure; a great group of capillaries gather in a zone of the vein and, all of them together, but independently, flow into the venous cavity. We observe this same fact constantly repeated and it is really the most common way in which the glomerular artery joins the vein. We can frequently observe these capillaries surrounding a stout venous vessel, in a crown-like way. Some other times, the arterial capillaries join in a very short venous vessel of sensible diameter that will also open into the wall of a stout vessel.

Though the junction through independent capillaries to a great vessel is the rule of the arteriovenous junctions, there is another type worth while mentioning: In figure 7 we can see a very curious lacunar disposition of arteriovenous junction. In fact, a thick vein, that seems to have its origin in this place, receives an abundant bunch of capillaries so much so, that, as they join, they form a small lacuna that flows directly into the vein, giving the impression that there is so great a number of arterial capillaries that they must reduce their surface to flow into the vein.

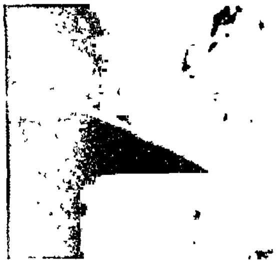

FIG. 8. Direct junction of glomerular artery to vein

These types of arteriovenous junctions, where the capillary network joins the vein directly, seem to be situated in the renal zones of more specific function, giving the impression that the glomerular arterial circulation would be favored by the action of a great pump, represented by the vein, to empty its content. Because though the venous system is poor in pressure of cm. of Hg, the sanguineous mass displaced towards the cava would absorb a great quantity of fluid from the capillary small canals, thus helping the renewal of the sanguineous flux.

Second group. In the second group we include all the glomerular vessels in which the postglomerular portion joins the venous system without any interposition of the so-called capillary net. This group must be divided into two subgroups:

Subgroup a. In this subgroup we shall assemble all those arterial formations of the glomerular artery, that pass directly into the venous system.

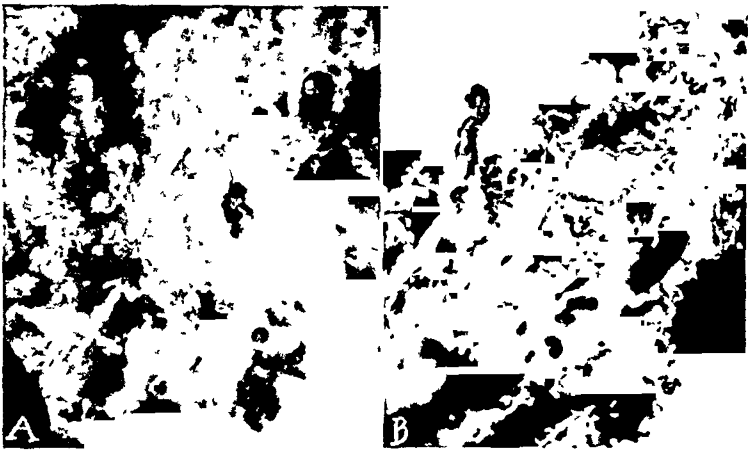

FIG. 5. *A*, panoramic view of arteriovenous junctions. *B*, photomicrograph of arteriovenous junctions.

arteriolary vessels gather around the extremities of those thick venous trunks. These vessels whirl and press around their joining point forming the arteriovenous junction.

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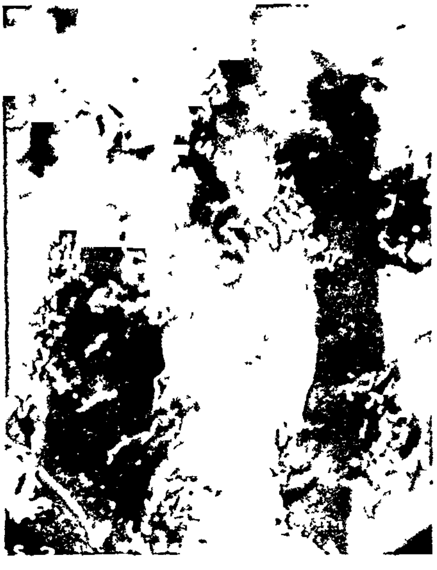

FIG. 6

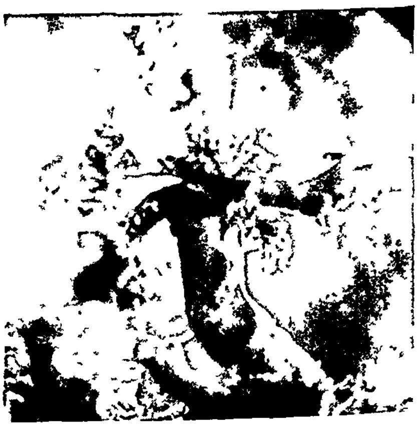

FIG 7

FIG. 6. Two stout venous vessels receive directly numberless capillaries, that sometimes gather in a vein of less caliber before joining major vein.

FIG. 7. Lacunar disposition of arterial capillaries before joining vein

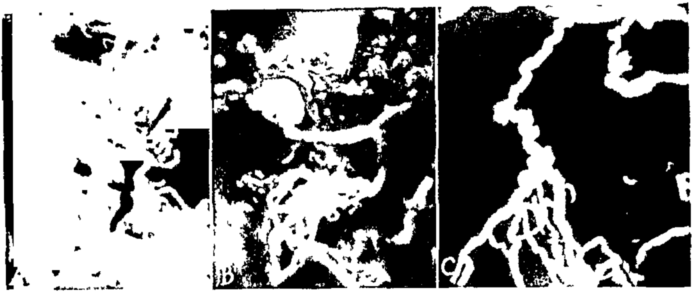

FIG. 11. *A*, direct junction of glomerular artery with small vein. *B*, glomerular artery divided in limited number of branches that join directly to veins of same size. *C*, two very small glomeruli with big arteries, one of them is divided in branches that join directly a small vein.

postglomerular portion, which in this case has a greater diameter than the preglomerular portion, divides in two small trunks; one of them branches into a limited group of six to ten arterioles, whose individual diameter is slightly smaller than that of the same glomerular artery: the diameter thus becoming in the whole much greater. All these arteries pass into the venous system through veins of the same diameter. It is particularly interesting to see that these formations are generally met with near the arcuate vein.

The same thing is shown in figure 11, *C*, in which glomerular arteries before ending in veins, give off a limited group of arterial branches. In this case we may observe a glomerular vessel whose postglomerular portion is, undoubtedly, of a much greater diameter than before forming the glomerulus. This artery gives off a group of arterioles which can be easily counted, that flow into a big vein or in other small veins of the arterioles size, before finding a drainage trunk. Notice the small size of the glomerulus which is practically reduced to a simple evagination that looks like an embryonic glomerulus.

Another interesting variety of this subgroup is formed by those glomerular

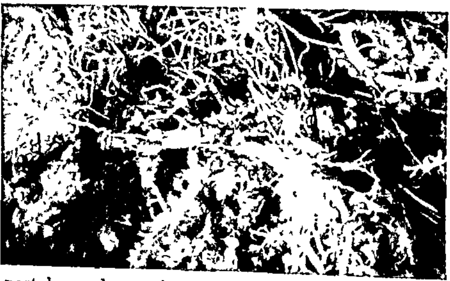

FIG. 12. Long postglomerular portion of artery divided in three branches before reaching vein.

arteries that, before joining the vein, will run a noticeable length. Some glomerular arteries, even ten times the diameter of the glomerulus as in figure 12, give off, further on, several arterioles; that will join each of them small veins to reintegrate their content to the general circulation.

COMMENTARY

The study of this small portion of the circulatory system of the kidney is of the greatest importance. To our belief, it actively contributes to the very important functions of clearance and secretion.

We have noticed, in the formerly described technique, that the plastic substance can be very easily injected into the artery, at the habitual pressure of a living man—that is up to 10 to 14 cm. of mercury, and that the excess of latex injected flows rapidly into the vein; while, if we perform this experiment injecting through the vein, we shall discover, practically at once, that the injected substance has stopped flowing. This shows us clearly that the circulatory continuity from vein to artery is practically impossible. That is to say that, in the kidney, we accept the general organic premise that the arterial blood flows into the vein, but that the venous blood does not flow into the artery. We have not seen valves that could easily explain this special progression of the blood. Nevertheless, if we come to think of the arteriovenous junction of the glomerular artery, we shall find the natural explanation to the difficulty of the venous progression towards the artery and the facility of the arterial progression towards the vein.

In fact, considering from the physical point of view the arteriovenous junction, we see that most of the glomerular arteries such as those included in the first group, join a venous trunk of great caliber through capillaries, or, sometimes, through very small veins. This means that the drainage must be much more easy from the capillary vessel to the vessel of great caliber and, consequently, very difficult the other way round.

On the other side, we must try to understand the two different great types of arteriovenous junction of the glomerular artery. Let us analyse the two great glomerular groups, such as we have considered them.

Group I. Glomerulus whose postglomerular arterial portion is divided forming a capillary network. What is the reason for the capillary network? Why does it join the vein so abruptly? Why is there a free trunk immediately after the glomerulus?

We must try to answer these questions thinking of the probabilities that might exist for the physiological action of urinary clearance. Let us consider this capillary reticle as an element interposed between the glomerulus and the vein, reticle through which all the convoluted tubules pass; proximal or distal tubules that belong to different glomeruli or to different renal zones. This zone, absolutely pierced, through which the tubules pass, is full of blood. Let us imagine that in this tubular reticle, the walls disappeared, changing into a sanguineous lacuna, lacuna through which all the depurative renal tubules will pass, intercrossing each other in all directions. It is absolutely clear that the only reason for this sanguineous lacuna must be purely and exclusively a special physiological labor.

If we think as classically that the postglomerular portion of the artery has contracted, a more abundant afflux of blood flows into the glomerulus and will force the filtration of all the sanguineous elements that will pass through the glomerular membrane and that will be eliminated within Bowman's capsule and then will consequently pass to the proximal convoluted tubules, following to Henle's loops and to the convoluted distal tubules. A defined increase of capsulo-tubular content takes place. This content has been extracted from the blood, as water or as electrolytes or as any other molecule whose passage is permitted by the glomerular membrane. Besides, the blood that flows on through the glomerular artery shall have now acquired such a hemoconcentration that when pouring into the lacuna, shall be in an osmotic tension much greater than that of the liquid within the tubule. If the tubules are soaked in all this blood, an osmotic unbalance is logical, thus favoring the absorption of the liquids that are in the convoluted urinary tubules, passing partly again to the blood, in order to restitute its osmotic balance. This will therefore secure the continuity of circulation towards the vein. We must bear in mind that all these capillaries generally open into larger venous trunks, that will behave in a pump-like manner, helping to drive the blood that is in the adjacent capillary lacuna.

The balance thus established, it is easy to understand the re-initiation of the process, that is to say, the new contraction of the arterial efferent portion of the glomerulus forcing again the filtrate through the glomerulus, the hemoconcentration of the blood in the capillary lacuna, and, once again, the osmotic unbalance that will have to equilibrate again through absorption.

We claim to consider this possible and acceptable. But, unfortunately, this has not been physiologically confirmed. Moreover, we do not deny that the urinary work is carried out by the cellules of the tubules, but we believe that it will be greatly favored with the equilibrium that must exist in every organism, as physic has proved.

That is why we are likely to believe that all the capillary net corresponding to the postglomerular portion of the artery must always have blood of arterial origin and that will only change into venous blood when it approaches the vein and when being free of the work of absorption, so to say, because of the increase in osmotic tension.

We must underline the great importance that this concept of the sanguineous lacuna has for pathology, the sanguineous lacuna absorbs what has been filtered through the glomerulus, that is to say that it produces a tubule-sanguineous state of equilibrium, restoring to the blood what this needs and leaving in the tubule the urinary clearance. Thus we understand the two types of anuria, be it by glomerular ischemia or by glomerular congestion. In the glomerular ischemia cases, when a persistent vaso-dilatation of the postglomerular portion of the artery occurs, there will be not any increase of pressure that might favor the filtration, and therefore the glomerulus will be empty of blood. In that case, blood will flow directly into the vein and there will not be any production of urine, because there is no unbalanced osmosis, the filtered blood having not passed through the glomerulus: the anuria will occur with ischemia of the glomerulus.

We can also explain, with the concept of capillary lacuna and the concept of the arteriovenous junction of the postglomerular portion of the artery, the anuria cases caused by renal congestion. If the venous lacuna is in a plethoric state with impossibility of evacuation because of a delay in the venous flood (cardiac insufficiency or contraction of the opening into the vein in the neurovegetative states or edema that might exist in endotheliums in allergical states, etc.) we shall have the lacuna subjected to blockade with considerable increase in the retained blood, extravasated edema, etc. These different states will cause the compression of the urinary tubules, producing anuria, not ischemial, but anuria of congestive and hemorrhagic glomerular type. In these cases, the glomeruli will be full of blood, blood that cannot flow; the tubules will be full of filtered liquid that cannot progress because they are compressed as they pass through the capillary lacuna.

Group II. Glomerular artery whose postglomerular portion joins the veins without interposition of capillary net. We have observed, especially near the juxtamedullar portion, that numerous postglomerular arteries have no interposition of capillary system between the glomerulus and the vein. All the more that may happen is a division in two, three or more branches of such artery that will open into the great renal vein or that will join a small straight renal vein to end, later on into the renal arcuate veins. Nevertheless, the glomeruli to which these arteries belong are perfectly functioning glomeruli. But it is true that there are some very small glomeruli; these small glomeruli exist when the diameter of the postglomerular artery is much greater than that of the preglomerular portion, that is to say, that a direct circulation establishes itself from the artery towards the vein, without urinary production because of a lack of glomerular filtrate. This does not mean to say that this glomerulus does not function. In other cases of an artery without interposition of capillary net, we observe big and perfectly functioning glomeruli. If we come to think that the uriniferous tubules of these glomeruli have no need at all that the blood that they filter should be cleared by their own capillary, but that can be re-absorbed by any other capillary system depending on another glomerulus, we can clearly see the possibility of the perfect functioning of such glomerulus under favorable circumstances. We interpret this fact as a means of parenchymatous defense.

No matter in what state of blockade the kidney might be, due to injuries that may alter the filtration in the capillary lacuna already described, the only way of conserving the renal economy is to divert the blood to make it flow straight into the vein, in order not to produce sanguineous compromising ectasia that might lead to the destruction of the nephrons, as tender as every organized tissue.

We believe that the study of the glomerular structure and especially the study of the structure of the whole arterioglomerular complex and its venous junction, in accordance to what we have found, opens a vast field, not only to the revision of the normal physiology of the organ, but also to the interpretation of renal disease, which is still so confused.

SUMMARY

In this study we show the morphological structure of the portion of the postglomerular part of the glomerular artery and its junction to the venous system.

Two great groups are described: one in which the arteriovenous junction is made by an independent capillary bed system for each artery. Most of the capillaries flow directly into the vein.

The other group joins the venous system without capillary bed interposition.

The first one is for physiological work. The second one is for the defense against pathological injuries.

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ELECTROLYTE THERAPY IN THE CONTROL OF UREMIA: WITH SPECIAL REFERENCE TO POSTOBSTRUCTIVE UREMIA

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Uremia and acidosis on the basis of renal dysfunction poses a very serious problem for medical management. Of utmost importance in such cases are control of infection, correction of dehydration and relief of any obstruction. Dramatic improvement is not unusual when these measures are properly exercised, but they are often inadequate for survival.

Within the past two years 84 patients suffering from uremia and acidosis on the basis of intrinsic renal disease have been treated with a combined electrolyte approach.[1-3] Specifically this has consisted of the administration of hypertonic sodium lactate (one molar or ½ molar) 120 to 240 mEq orally or intravenously daily, 4 to 8 gm. calcium gluconate intravenously or orally in a 10 per cent suspension of calcium lactate in amphojel and occasionally 20 to 80 mEq of potassium acetate (orally as a one molar solution or intravenously as potassium chloride). With this regimen varying degrees of clinical improvement were observed as well as frequent chemical improvement in a large percentage of the cases. The most striking changes noted were a fall in the blood urea nitrogen and serum chloride levels with a concomitant rise in the CO_2 combining power, this at times going as high as 55 mEq/L with no signs or symptoms of alkalosis.

Since 12 of these patients were seen in conjunction with the urologists, it is the purpose of this paper to report the chemical changes in the urea nitrogen with brief remarks on the clinical status in 10 patients of this group.

MATERIALS AND METHODS

The patients studied were all seen in conjunction with an attending urologist. No patient was seen until obstruction, dehydration and infection were alleviated. The patients were selected for the following reasons:

1) Prolonged drainage had failed to reduce the blood urea nitrogen level to the range where surgical intrervention could be employed for correction of the obstructive defect.

2) In spite of routine treatment a picture of progressive uremia was seen.

3) Patients were responding slowly to drainage where a chemical and clinical improvement might shorten the hospital stay.

4) All patients were believed to have intrinsic renal disease.

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In noncomatose patients baseline data were collected with the patients being placed on a 1.0 gm. sodium chloride, 20 gm. protein diet. In all cases daily or alternate daily determinations were done for blood urea nitrogen, sodium, potassium, chloride and CO_2 combining power. Careful fluid intakes were measured from 7 a.m. to 7 a.m. Twenty-four hour urines were collected from 7 a.m. to 7 a.m. and analysed for sodium, potassium, and chloride. Since all cases had a good urinary volume, fluid intake was kept between 2500 to 3000 cc daily orally or intravenously (or about 1000 cc above the output). The selection of intravenous fluids depended on the choice of the attending urologist.

Urea was determined by the urease method.[4] Sodium and potassium were analysed on a lithium Internal Standard Flame Photometer.[5] Chloride analyses, serum and urine were performed by the method of Schales and Schales.[6] CO_2 combining power was measured on a Van Slyke manometric apparatus.[7]

When possible the patients were weighed daily upon arising. Blood pressure was recorded twice daily routinely but every 20 minutes during the hypertonic intravenous solutions. A complete blood count and routine urinalyses as well as repeated urine cultures were made on each case. Most patients were maintained on antibiotic therapy during the baseline period.

The cases presented in this paper were treated according to the following schedule in regard to time and dosage of fluid and electrolytes.

In comatose cases, all therapy was given intravenously. Thus,

1) In the morning following withdrawal of blood for chemistries (10 a.m.) 1500 cc of 5 per cent glucose in water or 10 per cent travert* with 2 to 6 gm. calcium gluconate† (10 per cent solution) was administered in a two to two and one-half hour period. Potassium as acetate‡ or chloride 2 to 4 gm. was added to this infusion if the serum value was low or normal and if an adequate urinary volume was maintained, but when the serum potassium was elevated 10 units of regular insulin was included in the intravenous.

2) Never less than 3 or 4 hours after the aforementioned intravenous: (4 p.m.) 120 to 240 mEq of one‖ or ½ molar sodium lactate with 0.5 gm. aminophyllin was given slowly over a 1½ to 2 hour period with frequent checks of the blood pressure, pulse, and respiration. The 1 molar concentration was always used when edema was present or when cardiac embarrassment was suspected. When administered as one-half molar this was made up of equal parts 5 per cent glucose in water. The amount of sodium lactate was decided upon by the clinical response of the patient and the fall in the blood urea nitrogen value. Thus if an initial

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[4] Karr, W. G.: J. Lab. & Clin. Med., 9: 329, 1924.

[5] Fox, [illegible]

[6] Scha[illegible]

[7] Van [illegible]

* Baxter invert sugar.

† A personal communication from Dr. J. P. Peters indicates that perhaps calcium lactate or calcium chloride would be more efficacious since the yield of calcium from calcium gluconate is extremely small.

‡ Cutter Laboratories, Berkeley, California.

‖ 1 molar racemic sodium lactate–Eli Lilly Company available in 40 cc ampules. Thus 1 mEq = 1 cc. In this series the sodium lactate was never used as the recommended dilution to 1/6 molar.

TABLE 1

Patient	Age	Diagnosis	Initial BUN	BUN after Drainage & Time	Na Lactate Dosage/mEq	Time	Final BUN	Remarks
1. D.D.	78	Diabetes mellitus BPH	105	76 mg.% 4 weeks	1680	2 weeks	15	On Na. Lact. thru & after surgery. PSP—less than 5%. Urea clearance 100%, maintenance not necessary.
2. J.S.	67	Arteriosclerotic heart disease, BPH	100	70 mg.% 3 weeks	1600	10 days	29	Clinical & chem. deterioration rapid when lactate was discontinued. Autopsy: Generalized TB.
3. J.D.	51	Bilateral hydronephrosis; CA prostate	180	126 mg.% 3 weeks	3360	3 weeks	17	Died suddenly in electrolyte balance. No cause of death found at autopsy.
4. G.J.	60	CA prostate with metastases	173	61 mg.% 3 months	15,120	11 weeks	27	PSP—less than 5%. Marked improvement on treatment.
5. W.H.	78	CA prostate; HCVD*	135	61 mg.% 11 weeks	13,120	8 weeks	15	Excellent clinical response.
6. W.B.	75	CA prostate; HCVD*	60	160 mg.% 8 days	960	3 days	180	Received only oral sodium lactate. No response.
7. E.S.	29	Hypoplasia rt. kidney; hydronephrosis—left	30	Rising to 124	1420	9 days	10	Maintenance not necessary. Acute uremia, following dilatation.
8. J.C.	62	BPH, postobstructive uremia	66	48 mg.% 24 days	390	2 days	14	Terminal: dramatic response. No previous response to $NaHCO_3$.
9. W.S.	79	Postobstructive uremia; BPH	47	40 mg.% 21 days	1600	7 days	11	Remained on sodium lactate through and after surgery. Dramatic clinical response.
10. W.H.	71	Postobstructive uremia	47	45 mg.% 60 days	680	4 days	24.5	Remained on Na lactate through and after surgery.

* Hypertensive Cardiovascular Disease

drop in this value did not occur or if a falling level was not maintained, the dose was increased.

3) Never less than three to four hours after completion of the above hypertonic intravenous (10 p.m.), 1000–1500 cc of 5 per cent glucose in water or 10 per cent travert with 2 to 6 gm. calcium gluconate, 10 units of insulin was given. Potassium was added to this infusion as needed.

4) When the patient roused from coma and could tolerate oral feedings, the intake was maintained at 2500–3000 cc (assuming adequate urinary output) with water, tea and sugar, coke syrup, and ginger ale. Supplementary intravenous feedings were given if the fluid intake could not be maintained orally. The diet was gradually increased from salt free toast and butter, mashed potatoes, and hard candy to 1.0 gm. salt, 20 gm. protein.

5) As soon as possible oral electrolyte therapy was begun. Thus the management of noncomatose cases at this point was identical with the patient who roused from coma. Oral dosage schedule which was followed constituted:

a) 40 cc one molar sodium lactate* four to five times daily.

b) 20–40 cc 10 per cent calcium lactate in amphojel four times daily.

c) When necessary as judged by a falling serum value: 5–10 cc 1 molar potassium acetate† three to four times daily.

Serum potassium values were followed closely and a value rising to above normal values indicated that supplementary potassium should be stopped immediately.

This schedule was continued in four of the cases through surgery. When these patients became stabilized and remained in good clinical and chemical condition with withdrawal of electrolytes, all therapy was discontinued.

RESULTS

The results of this combined electrolyte regimen are summarized in table 1. Ten of 12 patients are presented who were treated in this fashion after varying periods on drainage. During the baseline period the obstruction, infection, and dehydration were controlled, and it was felt that these factors did not contribute to the elevation of the blood urea nitrogen when therapy was begun. Cases 3, 4, 6 and 8 were semicomatose and clinically terminal, while the other cases represented typical cases of chemical uremia after adequate drainage, excepting case 7 in which the patient was a rapidly progressing uremic after ureteral dilation for stricture. In this case, congenital hypoplasia of the opposite kidney was present. Age group seemed of no importance. Since the variables of calcium and potassium in noncomatose cases were ascertained to have no effect contributing to the elevated urea nitrogen, the effect of sodium lactate appeared to be specific. All cases showed a drop in the blood urea nitrogen, except case 6 in which the patient displayed a fulminating picture where therapy was completely ineffective. The total dosage and time interval varied in the successful cases, but six of the 10 cases showed a good response in a two-week period or less. Three cases required more intensive therapy and much larger doses of sodium lactate, making definite interpretation of the results difficult since the drainage period was also prolonged. In case 2 therapy was stopped and within a 7-day period there was a rapid rise in the urea nitrogen. Case 3 died suddenly after a dramatic clinical response and no explanation for sudden death was apparent at autopsy. Edema was noted in cases 1 and 4, but this was directly attributed to an increased sodium chloride intake. By withholding sodium chloride, the edema subsided although the sodium lactate was continued.

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* Special preparation Mr. Robert Bogash (Lennox Hill Hospital, New York City) made available through Libby Drug Company, Wilmington, Delaware.

† Prepared by Mr. Robert Bogash.

(Both preparations were made in a thick syrup so that full dosage would add 800 calories to the diet daily.)

DISCUSSION

Although sodium therapy may be frequently contra-indicated in uremia and acidosis due to renal dysfunction,[8, 9] its use in the hypertonic form with the lactate ion apparently benefited nine of the 10 cases presented. Four of these patients were comatose and in severe clinical and chemical uremia, having failed to benefit from usual methods of treatment. In these cases the clinical and chemical response was dramatic except case 6 in which the patient displayed a fulminating picture of uremia and expired. Since at that time no intravenous sodium lactate was available the medication was given to the patient through a Levine tube and perhaps the absorption from the gut was unsatisfactory. In several cases maintenance therapy appeared to be indicated to hold a rise urea nitrogen in abeyance. Case 2 showed a rapid rise in the blood urea associated with clinical deterioration immediately upon cessation of the sodium lactate, but this is difficult to evaluate since he suffered from systemic disease. Maintenance therapy has been decided upon by the criteria of a relapse with discontinuance of medication or renal function tests below 10 per cent of normal, as measured by the phenolsulfonphthalein and urea clearance determinations. All other patients showed some degree of clinical improvement with alertness and sense of well being, but since they were ambulatory the chemical changes seem to be more valid. Four cases eventually were operated upon, and with continued therapy in the postoperative period there was a satisfactory outcome in all.

Edema formation was noted in 2 cases, and it is of interest that these patients had obtained added salt, thus deviating from their diet. All medications were continued and with the only variable being withdrawal of the added sodium chloride, the edema disappeared spontaneously, perhaps indicating that chloride retention was at fault[10] or that the total sodium intake was in excess of the kidney's ability to handle it. Four patients had hypertension complicating their renal disease, and the large doses of sodium did not aggravate this condition.[11] In no case was pulmonary edema produced from the large doses of the hypertonic sodium lactate.

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[11] Friedberg, C. K.: Diseases of the Heart. Philadelphia: W. B. Saunders Co., 1950, p. 94.

The fate of the blood urea nitrogen is not clear, and the decreasing blood urea may have resulted from an increased urinary excretion of urea nitrogen. Present studies indicate that at times this is not always true; thus the possibilities of decreased formation or alteration on the chemical structure of urea must be entertained.

The main alterations in the structure of the extracellular fluid were in regard to the chloride, bicarbonate relationship. The serum sodium values were normal except in two cases where they were low. With therapy these values increased but did not reach normal levels. Urinary sodium values were variable in the baseline period depending upon diet and previous treatment but in nearly all cases were low, thus ruling out a salt-losing nephritis and perhaps indicating a conservative mechanism in the kidney tubules.[12, 13] Sodium was apparently retained initially in most cases to varying degrees, and in all cases with the administration of sodium lactate the excretion of sodium in the urine rose to much higher levels frequently approximating normality. From these values it was felt that regardless of the renal disease, sodium could be handled in a better manner when given as lactate in the hypertonic form.[1] Salt loads were not previously given to these patients because of their clinical condition.

The potassium values in the serum were high in four cases, as is frequently seen in uremia.[14-16] On forced calories, sodium lactate, and calcium lactate therapy all cases displayed a fall in the serum potassium levels. When this potassium value was below normal, 1 molar potassium acetate was administered orally in doses adequate to restore this value to normal. Urinary potassium excretion was low in all cases (10 to 25 mEq/L) indicating tubular dysfunction for the excretion and secretion of this ion.[17-19] All cases showed some uptake of potassium and this may have been in keeping with their clinical picture since they were then better able to eat. The fact that sodium and potassium were retained suggests the possibility of a body base deficit in uremia[20, 21] as was noted with tissue analyses.[22, 23]

All cases showed a normal or high normal serum chloride value,[24] and with the added lactate all cases but one showed a decrease in this value. Two cases remained within the range of normal. Five cases dropped below 100 mEq/L. Of

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[18] Platt, R.: Lancet, 1: 1239, 1951.

[19] Mudge, G. H. [illegible] er. Biol. & Med., 76: 545, 1948.

[20] Gamble, J [illegible]

[21] Hartmann [illegible] Investig., 1: 359, 1925.

[22] Porter, R. [illegible] : 127, 1928. [illegible] N. F.: J. Am. Clin. & Clin. Assoc., 62: 1950.

[23] Baldwin, D., Robinson, P. K., Zierler, K. L. and Lilienthal, J. L.: J. Clin. Investig., 31: 850, 1952.

[24] Atchley, D. W. and Benedict, E. M.: J. Clin. Investig., 9: 265, 1930.

this group two cases fell below 80 but stayed above 70 mEq/L. None of these cases showed a marked chloro-euresis.[25]

The degree of acidosis varied in all cases; CO_2 combining power levels ranged between 6.3 to 18 mEq/L. This was changed upon administration of sodium lactate. The CO_2 combining power returned to normal in one case. Case 4 showed correction from 7.2 to 13.1 mEq/L before death. The remaining cases presented overcorrection of the CO_2 combining power to levels ranging between 32 and 36 mEq/L. No tetany was observed in these cases as adequate calcium was administered.

The exact mechanisms whereby the clinical and chemical improvement was effected are not clear. The changes encountered are not dissimilar from previously reported alkali therapy in tubular acidosis[26] and in the chloride acidosis resultant from ureteral transplants.[27, 28] Whether bicarbonate would be as effective in renal disease is not known, but much literature in the past would indicate that this would not always be true.[29-34] Lactate is a rapid precursor to bicarbonate and its place in the Krebs cycle may be of importance.[35] It is a potent source of energy for the liver and is rapidly metabolized by the brain.[36] Recently its specific effect on the renal tubular transport system has been described.[37, 38] Sodium in this form offered an available source of body base, and with the natural history of the disease, one may readily see how a cation deficiency could develop from poor nutrition, salt restriction, and nausea and vomiting and loss of fixed base due to renal acidosis.[20] When this was corrected and sodium then recovered in the urine, perhaps the added base and lactate replaced or abetted the ammonium-forming mechanism in the kidney. The excretion of an equiosmotic urine for sodium is believed to be desirable from the standpoint of expenditure of renal energy, and with sodium in this form all cases did more closely approximate this situation.[39] Although chemical changes were effected and clinical improvement resulted, one cannot state that there was an improvement in actual renal function. Since this type of approach is still investigative in nature it should not be used indiscriminately when adequate laboratory facilities are not available.

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[25] Pitts, R. F. and Lotspeich, W. D.: Am. J. Physiol., **147**: 138, 1946.

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[33] Weiss, E.: Med. Clinics North Amer., **23**: 1707, 1939.

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[37] Cross, R. J. and Taggart, J. V.: Am. J. Physiol., **161**: 181, 1950.

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[39] Newburgh, L. H.: Bull. New York Acad. Med., **24**: 137, 1948.

SUMMARY

A combined electrolyte approach to the control of postobstructive uremia has been presented. This has consisted of the administration of hypertonic sodium lactate along with calcium and occasionally potassium salts.

This regimen was associated with certain chemical and clinical improvement in most cases studied.

When sodium was administered in large doses as hypertonic sodium lactate it was found that the kidney could handle sodium in a nearly normal fashion regardless of the type or degree of kidney disease. The final efficacy of this therapy will depend upon its reproducibility in the hands of other investigators.

Grateful acknowledgment is made to the urologists who made this study possible. The technical assistance of Miss Elizabeth Garrigues, B. A., who performed the many analyses, is also acknowledged.

this group two cases fell below 80 but stayed above 70 mEq/L. None of these cases showed a marked chloro-euresis.[25]

The degree of acidosis varied in all cases; CO_2 combining power levels ranged between 6.3 to 18 mEq/L. This was changed upon administration of sodium lactate. The CO_2 combining power returned to normal in one case. Case 4 showed correction from 7.2 to 13.1 mEq/L before death. The remaining cases presented overcorrection of the CO_2 combining power to levels ranging between 32 and 36 mEq/L. No tetany was observed in these cases as adequate calcium was administered.

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[26] Dawson, J., Dempsey, E., Bartter, F., Leaf, A. and Albright, F.: Metabolism, **2**: 225, 1953.

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[33] Weiss, E.: Med. Clinics North Amer., **23**: 1707, 1939.

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[38] McDonald, R. K., Shock, N. W. and Yiengs, M. J.: Proc. Soc. Exper. Biol. & Med., **77**: 686, 1951.

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peritoneal lavage, it has been possible to maintain life in bilaterally nephrectomized dogs for 40 days,[4] 69 days,[5] and 110 days.[6] Vanatta, Muirhead and Grollman have logically concluded that the clinical picture of uremia is due to accumulation of retention products since it is relieved by their removal by dialysis.[7] These results also indicate that excretion of retention products and regulation of electrolytes are of primary importance for maintenance of life; and other metabolic functions, such as "two consecutive beta oxidations of fatty acids"[8] and formation of ammonia, are of lesser importance.

One metabolic function of the kidney, which is poorly understood and defined, probably cannot be replaced by the dialyzing method. It is the function that serves to maintain normal blood pressures. The hypertension and cardiovascular disease that follow bilateral nephrectomy[4] are supposedly due to lack of this kidney function.[9]

GENERAL PRINCIPLES OF THE TREATMENT OF UREMIA

It would be unfortunate if the medical management of uremia were neglected due to overemphasis on the use of the artificial kidney. The over-all management of uremia may be summarized as follows:

1) Restriction of fluid and electrolytes during the period of anuria.

2) Suppression of protein catabolism by forced administration of a high caloric regimen (Borst principle).[10, 11]

3) Prevention or treatment of infection with antibiotics.

4) Avoidance of elective surgery, excessive transfusion, and other procedures which may increase protein catabolism and the production of retention products.

5) Removal of retention products and correction of body chemistry by dialysis (artificial kidney, peritoneal lavage and intestinal lavage).

PRINCIPLE OF THE ARTIFICIAL KIDNEY

The principle of most artificial kidneys is the same today as it was in 1912 when the procedure was introduced by Abel, Rowntree and Turner.[12] Clotting of blood in the apparatus is prevented by heparin. Blood is withdrawn either with a pump from a large vein or taken from an artery and guided through a system of dialyzing membranes (tubes or sheets) with blood on one side of the membrane and the rinsing fluid on the other side. Dialysis, which means purification by diffusion through a semipermeable membrane, then occurs. (Graham 1861). Molecules of small size pass through the membrane; large molecules and blood cells do not. Fortunately, all known retention products, such as urea, uric acid, creatinine and phenols, are able to pass through the membrane. Their relative dialysis has been determined by Wolf and associates.[13]

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[5] Grollman, A., Turner, L. B. and McLean, J. A.: Intermittent peritoneal lavage in nephrectomized dogs and its application to the human being. A.M.A. Arch. Int. Med., 87: 379, 1951.

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[8] Sn[illegible] B-oxidation in [illegible]

[9] Grollman, A., Muirhead, E. E. and Vanatta, J.: Role of kidney in pathogenesis of hypertension as determined by a study of the effects of bilateral nephrectomy and other experimental procedures on the blood pressure of the dog. Am. J. Physiol., 157: 21, 1949.

[10] Kolff, W. J.: Forced high caloric, low protein diet and the treatment of uremia. Am. J. Med., 12: 667, 1952.

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[12] Abel, J. J., Rowntree, L. G. and Turner, B. B.: On removal of diffusible substances from the circulating blood of living animals by dialysis. J. Pharmacol. & Exper. Therap., 5: 275, 1913–1914.

Electrolyte equilibrium between blood and rinsing fluid occurs if dialysis is continued for a sufficient period of time. The plasma electrolyte content can be changed at will by varying the composition of the rinsing fluid.

The dual function of the artificial kidney is beautifully illustrated in the treatment of acidosis. First, acid retention products pass through the membrane into the rinsing fluid. Second, a shortage of cations is corrected as Na diffuses into the blood until equilibrium with the rinsing fluid is obtained. The end result is correction of the acidosis and establishment of normal electrolyte content of the blood.

With most artificial kidneys now in use there is a continuous flow of 12 L. of blood per hour through the apparatus. The reduction of blood urea from high to nearly normal levels requires from 5 to 12 hours of treatment. Large amounts of urea and other retention products can be removed. We once removed 263 gm. of urea in one dialysis. Dialysis may be repeated, if necessary, after 4 or 5 days.

TYPES OF ARTIFICIAL KIDNEYS

1) *Artificial kidneys using dialysis only.* These include Kolff's rotating artificial kidney which will be discussed later, and Guarino's[14] type which is new and now in the process of being tested. Both types use cellophane tubing.

2) *Artificial kidneys wherein the blood is pressed through a dialyzing system.* Filtration as well as dialysis occurs depending on the pressure gradient between blood and rinsing fluid in this type of apparatus. Some[12, 15-17] are more or less monumental relics of the preclinical period. The kidneys made by Alwall,[18] Murray,[19, 20] Rosenak,[24] Bodo von Garrelts,[21] MacNeill[22] and Kolff's stationary

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[14] Guarino, J. R. and Guarino, L. J.: Artificial kidney—a simplified apparatus. Science, **115**: 285, 1952.

[15] Haas, G.: Die Methodik der Blutauswaschung (dialysis in vivo). Abderhaldens Handbuch der Biologischen Arbeitsmethoden Abt. V. Teil **8**: 717, (Berl.) 1935.

[16] Necheles, H.: Dialysis of moving blood stream. Klin. Wchnschr., **2**: 1257, 1923.

[17] Thalhimer, W.: Experimental exchange transfusions for reducing azotemia; use of artificial kidney for this purpose. Proc. Soc. Exper. Biol. & Med., **37**: 641, 1938.

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[19] Lam, C. R. and Ponka, J. L.: Experience with Murray artificial kidney. J. Lab. & Clin. Med., **32**: 1434, 1947.

[20] Murray, G., Delorme, E. and Thomas, N.: Development of artificial kidney. Arch. Surg., **55**: 505, 1947.

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[22] MacNeill, A. E.: Further development of small, compact and efficient blood dialyzer for military use. Presented at a meeting of Subcommittee on Cardiovascular Diseases of the Committee on Medicine, National Research Council, March 18, 1953.

type[21] [23] use cellophane tubing compressed either between screens[24] or grids[18] [21] [22] or tubes of small diameter[20] to keep the blood volume as low as possible Skeggs, Leonard and Heisler,[25] [26] Lowsley and Kirwin[27] use cellophane sheets sandwiched between grooved plates

3) *Artificial kidneys using filtration only* Malinow and Korzon[28] built an apparatus by which large amounts of ultrafiltrate can be removed, in terms of clearance it is far inferior to the dialyzing machines

4) *Artificial kidneys using resins* Muirhead and Reid[29] have demonstrated their possible use, and de Marchi and Bronnimann[30] had encouraging clinical experiences with a resin type artificial kidney Careful conditioning of the resin bed is necessary to prevent undue absorption or elution of electrolytes This approach is even more promising as new and better resins are being developed

EFFICIENCY OF ARTIFICIAL KIDNEYS

The efficiency of artificial kidneys is usually expressed in terms of clearance The urea clearance of the rotating kidney at a flow rate of 200 ml per minute is 170 ml per minute[31] The urea clearance of the Skeggs, Leonards and Heisler kidney is 125 ml per minute at the same flow rate The clearance of all other artificial kidneys is less High clearances of urea are desirable because the clearance for most other solutes is much less With urea clearance as a basis of comparison, clearance of uric acid is only 45 per cent, clearances of inorganic phosphate and sulfate are 32 per cent each, and the clearance of phenol red is only 11 per cent[13]

Rotating type of artificial kidney In figure 1 blood comes from the radial artery and passes first through a flow meter,* then through a rotation coupling and into the cellophane tubing† which is spirally wrapped around a rotating drum While the drum rotates, at 25 revolutions per minute, the blood seeks the lowest level

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[29] Muirhead, E E and Reid, A F Resin artificial kidney J Lab & Clin Med , 33 841, 1948

[30] de Marchi, A and Bronnimann, R Construction d'un rein artificiel basé sur les propriétés physico chimiques des résines synthétiques, résultats préliminaires Helv chir Acta 18 133-145 1951

[31] Merrill, J P , Thorn, G W , Walter, C W Callahan, E J , III and Hollingsworth Smith L , Jr The use of an artificial kidney, I Technique J Clin Investigation, 29 412, 1950

* Fisher and Porter Flow Rater #B 2 A-127 with ¼ inch diameter glass ball Hatboro, Pa

† The dialysing tubing 20/32 or 23/32 inch inflated diameter is made by Visking Corporation, 6733 W 65th St , Chicago, Illinois

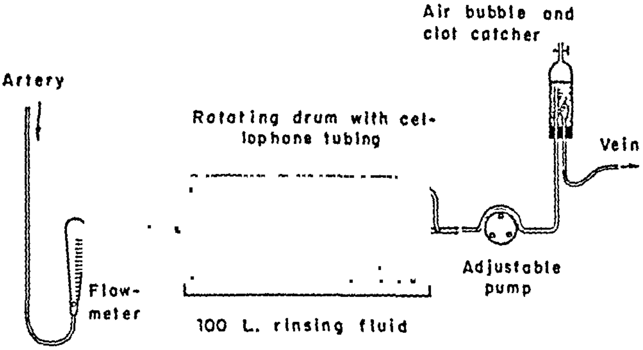
Air bubble and clot catcher
Artery
Rotating drum with cellophane tubing
Vein
Flow-meter
Adjustable pump
100 L. rinsing fluid

FIG. 1. Diagram of rotating kidney. Blood comes from radial artery, rate of flow is measured by flow rater and controlled with screw clamp. Blood passes through hollow axle of drum and enters cellophane tube. Once in cellophane tubing it moves by gravity when drum rotates. Cellophane tube is not filled like a sausage; just a thin film of blood moves through cellophane. Roller pump returns blood to a vein of patient.

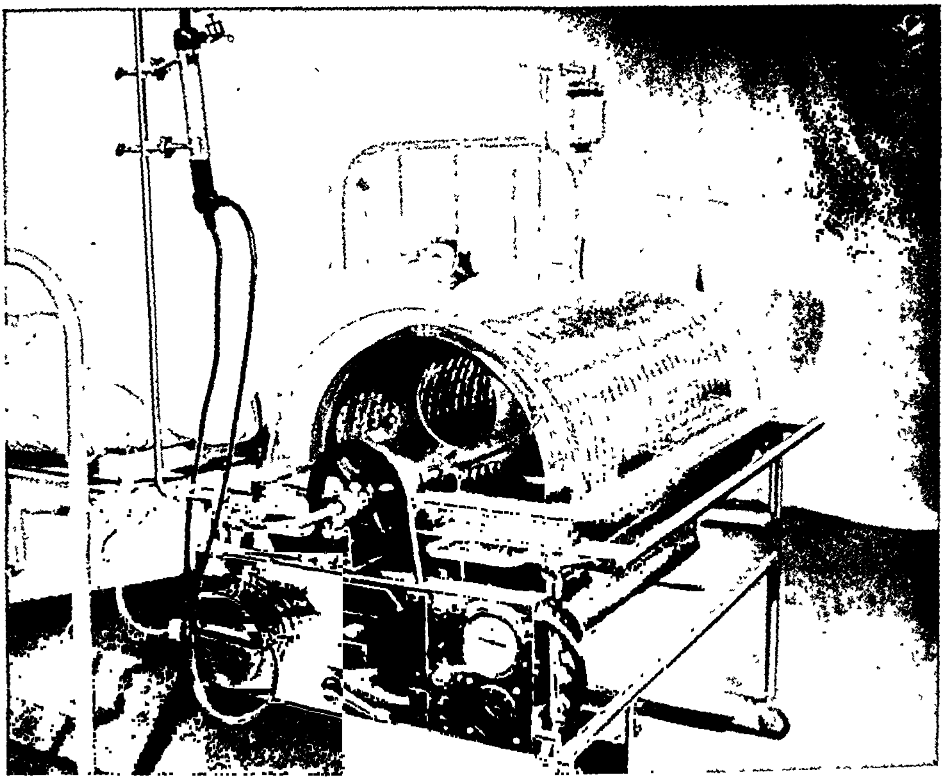

FIG. 2. Rotating type artificial kidney made by Allis-Chalmers. (Reproduced with permission of Mr. H. K. Ihrig, Vice-President, Allis-Chalmers.) Cellophane tubing (sausage casing) is wrapped around a stainless steel cylinder. Through lucite hood, one can see last loop of cellophane tubing where it is connected to outflow tube for blood on upper part of cylinder. Outflow tube then proceeds to axle of drum in which a rotation coupling is mounted. Blood is pumped back via a bubble trap (upper left) into vein of patient. Roller type pump is on lower left. Inflow for blood coming from radial artery is on other side of artificial kidney. Cylinder rotates with its lower segment through a bath. Rotation is slow, 25 revolutions per minute. Constant movement of both blood and rinsing fluid is important for good dialysis. Temperature of bath is thermostatically controlled. All parts in contact with blood can be removed and autoclaved.

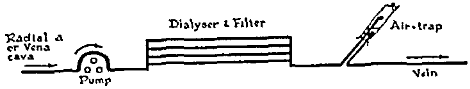

FIG. 3. Diagram of filtering and dialyzing type of artificial kidney. Pump to left forces blood through a system of dialyzing membranes. Rinsing fluid (not shown) circulates on outside of membranes. As blood is under pressure, dialysis and filtration take place.

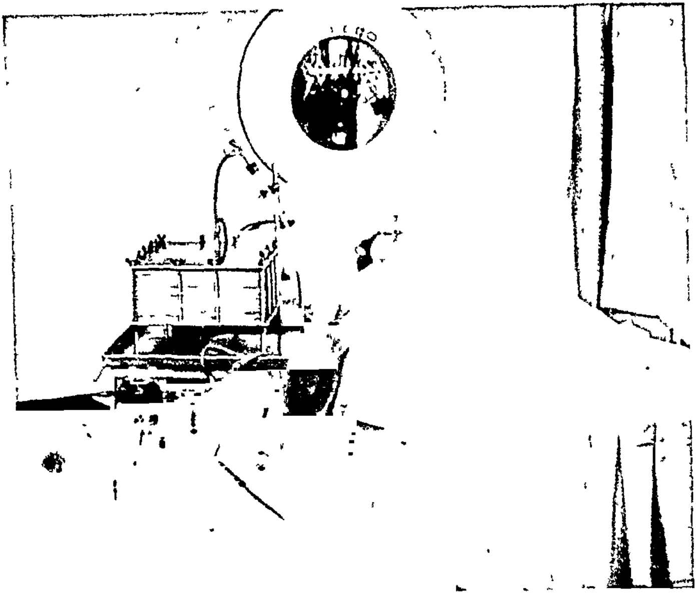

FIG. 4. Stationary artificial kidney by Skeggs, Leonards and Heisler Tank with rinsing fluid to left Pump for rinsing fluid and heater is inside cabinet. Pump for blood projects in front of cabinet T[illegible] cava via a cannula inserted in saphenous vein [illegible] cabinet Cellophane sheets [illegible] od flows through space between [illegible] between cellophane and rubber [illegible] is placed on scale As this type of kidney is filtrating and dialyzing, a scale is useful to control loss of weight of patient or to weigh combined tanks of inflow and outflow fluid which reflects total fluid removed.

in the cellophane tubing and consequently runs through the spiral from left to right. Thus the tubing on the bottom half of the drum is only partly filled and a film of blood remains in the collapsed cellophane tubing on the upper half of the drum. There cannot be much difference in hydrostatic pressure inside and outside the cellophane tubing, and there is no filtration. At the end of the cellophane tubing, blood enters a plastic tube and leaves the artificial kidney through another rotating coupling in the hollow axle of the drum. With the assistance of a pump it is then returned to a vein after passing through a clot and bubble catcher (fig. 2).*

Stationary type of artificial kidney (dialysis and filtration). Figure 3 indicates the manner in which blood is passed through the system of cellophane sheets or cellophane tubes either by arterial pressure or by a pump. The rinsing fluid flows on the outside of the cellophane membranes and the membranes are supported by screens, plastic or rubber ridges; otherwise the blood volume would be very inconstant. The artificial kidney by Skeggs, Leonards and Heisler, model 2 (fig. 4)[26] consists of cellophane sheets sandwiched between grooved rubber plates. This apparatus can be used as an ultrafilter when positive pressure is applied against the blood or suction to the rinsing fluid.

TECHNIQUE OF EXTRACORPOREAL DIALYSIS

It is not the purpose of this report to give detailed instructions for the assembling of artificial kidneys,[1,32] but some points of general interest will be discussed.

The artificial kidney team should consist of a technician to operate the apparatus, a technician to perform the different chemical determinations, in particular the clotting time, a nurse to insure the patient's comfort, and a physician to supervise the team and perform such procedures as cannulizations.

New cellophane tubing or membranes are used for each patient. It is possible that cellophane contains substances that cause chills, fall in blood pressure and other undesirable reactions. Some have advocated chemical treatment[7] others[33] prolonged boiling to remove these substances. We boil the cellophane tubing for 2 hours on a wooden reel that allows the boiling water to reach every part of the tubing. It must be stated however that in emergencies (and in numerous experiments on dogs) we have used cellophane tubing without boiling and that we have observed no ill effects. The tubing is perhaps less harmful than the membrane

All glass parts, except the flow meter are coated with silicone† to make the surface water repellent. This and the use of dispensable polyvinyl chloride tubing (tygon) instead of rubber helps to minimize the required amount of heparin.

After assembling the artificial kidney we fill it with zephiran for sterilization. It remains filled with zephiran and ready for use at any time. The artificial kidney of Skeggs, Leonards and Heisler can be sterilized with steam. Others prefer to keep most parts which come in contact with blood in a kit that can be sterilized in an autoclave;[32] the other few items are sterilized by zephiran.

We rinse the artificial kidney with 20 L. sterile water and a few liters saline to remove the zephiran, it is checked for leaks and then primed with 500 ml. fresh matched bank blood to which heparin has been added.

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* Variants of Kolff's rotating type of artificial kidney are produced by Olsen (Edward A. Olsen, Main St., Ashland, Mass.) and Allis-Chalmers. (Allis-Chalmers, Milwaukee, Wis.). For detailed plans of construction, see reference 1.

[32] Murphy, W. P., Jr., Swan, R. C., Jr., Walter, C. W., Weller, J. M. and Merrill, J. P.: Use of artificial kidney III. Current procedures in clinical hemodialysis. J. Lab. & Clin. Med., 40: 436, 1952.

[33] Skeggs, L. T., Jr., Leonards, J. R., Heisler, C. R. and Kahn, J. R.: Artificial kidney III. Elimination of vasodepressor effects due to cellophane. J. Lab. & Clin. Med., 36: 272, 1950.

† Dow Corning panglaze 2 per cent in carbon tetrachloride, bake 20 min. at 400°C, Dow Corning, Midland, Mich.

While the kidney is being prepared the blood vessels to be cannulated are exposed. We prefer to use the radial artery rather than cannulization of the vena cava inferior via the saphenous vein. The cutdown wound for the radial artery need not exceed 1½ cm. The radial artery has been ligated in hundreds of cases without trouble The same radial artery may be exposed 3 cm higher and used for the next treatment. With a proper cannula[1, 2] flow of blood from the radial artery usually exceeds 200 ml. per hour; flow is adjusted with a screw-clamp and measured with a flow rater. The blood is re-introduced into a cannulated peripheral vein (the cubital veins are always saved). At the end of treatment one might be tempted to re-infuse the blood present in the apparatus into the patient. However, the introduction of 500 to 700 ml. of blood into these patients at the end of the dialysis entails the risk of overloading the circulation, followed by pulmonary edema a few hours later.

HEPARIN

Initially, 80 to 120 mg. (8000 to 12,000 units) of heparin are given to the patient and 40 mg. are added to the 500 cc of citrated bank blood used to prime the artificial kidney. The aim is to maintain clotting time at approximately 20 minutes with *hourly injection of 5, 10 or 20 mg. of heparin. During the last* hours of the dialysis, a clotting time of 12 minutes is permitted.

RINSING FLUID

Composition of typical rinsing fluid is presented in table 1. Lactic acid is added to bring the pH to 7.4 where it is maintained by blowing a constant stream of 10 per cent CO_2 in oxygen through the rinsing fluid or under the hood of the artificial kidney. If the pH rises, calcium in the rinsing fluid is gradually precipitated as calcium carbonate.

TABLE 1. *Composition of rinsing fluid*

	Mg %		Na^+	K^+	Ca^{++}	Mg^{++}	Cl'	HCO_3' in mEq/L
NaCl	600	=	102				102	
$NaHCO_3$	250	=	30					30
KCl	40	=		5			5	
$CaCl_2$	28	=			5		5	
$MgCl_2$	15	=				3	3	
Total			132	5	5	3 +	115	30 + mEq/L
			145				145	
Total			290 mEq/liter or 286 mOsm/liter					
1% glucose 1000								56 mOsm/L
2% glucose 2000								112 mOsm/L
3% glucose 3000								168 mOsm/L

Lactic acid is added to adjust pH to 7.4

Glucose is added to the rinsing fluid for the following reasons:

1) To compensate for the osmotic pressure of urea and the colloid-osmotic pressure of the plasma proteins. Glucose concentration of 0.75 per cent in the rinsing fluid will lead to approximate water balance in the average patient treated with the dialyzing type of artificial kidney. The removal of edema with higher concentrations is discussed later.

2) To supply calories.

POSSIBLE DANGERS, COMPLICATIONS AND UNDESIRABLE EFFECTS OF TREATMENT WITH THE ARTIFICIAL KIDNEY

The early problems of the artificial kidney, hemolysis, clotting and shock, have been largely overcome and are now rare if technique is skillful.

1) *Pyrogenic reactions* have been virtually eliminated by use of new polyvinyl chloride tubing (instead of rubber tubing) and, of course, new boiled cellophane for each patient.

2) *Hemorrhage.* Polyvinyl chloride tubing and silicone coated glass have reduced the amount of heparin required. As a result, the former major danger of hemorrhage is now rarely encountered.

Despite heparinization during dialysis, hemorrhagic diathesis, often seen in uremia and evidenced by subcutaneous or oral hemorrhage, usually responds well to treatment with the artificial kidney. It is possible that the blood used to fill the artificial kidney plays a role.

3) *Change in blood volume.* The volume of blood in the cellophane tubing of the rotating type of artificial kidney is influenced by the flow rate from the artery. Thus at a flow rate of 200 the blood volume is 560 ml.[13]* With the use of a flow meter, changes in blood flow, and consequently in blood volume, are easily detected.

The blood volume in the stationary artificial kidneys depends on the distention of the cellophane. Concurrent with changes in pressure in the blood and rinsing fluid compartments are changes in volume.

4) *Technical error.* Technical errors could be fatal. Bleeding into the distensible cellophane tubing if the outflow of the kidney were blocked in the rotating type of kidney, or bleeding through a hole in the cellophane into the dialyzing fluid in any type of kidney could be fatal and continuous supervision is necessary.

5) *Hemolysis.* High temperature of the rinsing fluid or omission of salt from the rinsing fluid will cause hemolysis within two minutes. It is wise to mix and centrifuge a few drops of blood with rinsing fluid to detect error in composition of the fluid before the patient is connected. A mild degree of hemolysis cannot always be prevented when the rotating type of kidney is used. Usually it is barely visible. Unfortunate consequences so far have not been apparent.

6) *Morphologic changes in the blood.* Leukopenia usually occurs during treatment with dialysis but after a few hours the blood count returns to normal. De Leeuw and Blaustein[34] have shown that the leukocytes adhere to the cellophane;

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* At 25 revolutions per minute and 26 cellophane threads in the Archimedes screw.

[34] deLeeuw, N. K. M. and Blaustein, A.: Studies of blood passed through artificial kidney. Blood, 4: 653, 1949.

the thrombocyte count is often temporarily decreased probably for the same reason.

7) *Hypertension.*[35] When blood flow through the apparatus is 200 ml. or more per minute, a rise in blood pressure is frequently observed and is sometimes alarming. With lower flow rates it is rare. The rise in blood pressure can, if necessary, be immediately reduced with hexamethonium or by draining 300 ml. of blood into a burette along the inflow of the artificial kidney.

8) *Relative urinary suppression.* In patients with chronic uremia, urine output may diminish on the day of and on the day following treatment with the artificial kidney. It will be interesting to observe whether newer types of artificial kidneys will cause this temporary diminished urine output.

9) *Pulmonary complications.* Bronchopneumonia and pulmonary edema should not be listed as complications of treatment with the artificial kidney. On the contrary, they are usually improved by dialysis which both removes pulmonary edema[1, 31, 36] and makes the patient more alert so that he will cough. Pulmonary complications may result from a suppressed cough reflex due to oversedation; codeine should not be used. Pneumonitis or poor expectoration with subsequent anoxia is often responsible for death in patients debilitated by uremia.

INDICATIONS FOR TREATMENT WITH THE ARTIFICIAL KIDNEY

At what time during uremia should treatment with the artificial kidney begin? There are two schools of thought depending partly on the facilities available. In Boston, where an artificial kidney and team are available at any time, dialysis is used early in the course of uremia.[37–39] Dangers of such treatment are negligible, and the clinical course of the disease is much more mild if uremia is relieved early. This is especially true in older patients prone to pulmonary and other complications incident to prolonged bed rest. The other approach is dictated largely by the fact that use of the artificial kidney interrupts the work of busy physicians and entails considerable expense. Thus, the artificial kidney is not employed unless it appears dangerous to wait. The artificial kidney is used only when 1) blood urea level is between 300 and 400 mg. per hundred ml.; 2) serum potassium level is higher than 7 mEq/L.; and 3) a CO_2 combining power is less than 12 mEq.

The position of both groups is justified, and the present authors prefer the middle of the road.

The clinical conditions of patients with uremia differ immensely even if they have identical levels of retention products. The clinical condition is an important factor in determining whether treatment with the artificial kidney should be started. Characteristics of severe uremia may be progressive restlessness, irrational behavior or stupor. These symptoms are often promptly relieved after dialysis. One should not wait until a patient is completely comatose before employing the artificial kidney. Pulmonary edema and cardiac failure have often been improved by immediate dialysis.[1, 31, 36] The extreme abdominal distention often accompanying uremia also subsides promptly after dialysis. Vomiting, which frequently makes all oral intake impossible, is nearly always less or absent after dialysis.

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[35] Haynes, F. W., Merrill, J. P. and Goodale, W. T.: Plasma renin concentration of patients treated with artificial kidney. Fed Proc., 11: 67, 1952.

[36] Fishman, A. P., Kroop, I. G., Leiter, H. E. and Hyman, A.: Experiences with Kolff artificial kidney. Am. J. Med., 7: 15, 1949.

[37] Merrill, J. P.: Medical progress; artificial kidney. New Eng. J. Med., 246: 17, 1952.

[38] Merrill, J. P.: Use of artificial kidney in treatment of uremia. Bull. New York Acad. Med., 28: 523, 1952.

[39] Merrill, J. P., Smith, S., III, Callahan, E. J., III and Thorn, G. W.: Use of artificial kidney: clinical experience. J. Clin. Investigation, 29: 425, 1950.

Potassium intoxication rarely occurs without severe renal impairment and for this reason it is discussed here and not under the intoxications. Potassium intoxication can be relieved promptly by the artificial kidney.[1, 40] The changes in the electrocardiogram[41] are reversed during the dialysis and several authors[39] have assumed that the dialysis saved the patient's life.

The conditions listed that indicate treatment with the artificial kidney may occur in the course of acute or chronic uremia, independent of their cause. Some intoxications and edema in themselves occasionally provide an indication for use of the artificial kidney.

CONDITIONS LEADING TO THE INDICATIONS FOR USE OF ARTIFICIAL KIDNEY

1) *Acute uremia.** Ischemuric episode;[42] anuria following transfusion accidents, crush syndrome, shock, burns, or major operation and hepatorenal syndrome: These conditions are often erroneously called lower nephron nephrosis. Symmetrical cortical necrosis is probably an extreme form of this same syndrome.

Nephrotoxic poisoning (e.g. mercury, carbon tetrachloride and sulfonamides):[43] Some poisons may cause urinary suppression but little kidney damage (e.g. salicylate poisoning). The poison may be dialyzable. (See later.)

Acute glomerulonephritis in the earlier stage of the disease should not be treated with the artificial kidney as Merrill[38] has observed convulsions in such patients after dialysis. However, our results in the late stage of severe acute glomerulonephritis have been encouraging.[1, 2] Treatment of uremia secondary to subacute glomerulonephritis with progressive oliguria is invariably unsatisfactory.[1]

2) *Acute exacerbation of chronic uremia.* Whether this is caused by an exacerbation of a chronic nephritis or by an intercurrent infection, operation or intoxication, it should be treated exactly like acute uremia. Equilibrium may be restored so that a useful life is possible despite persistent chronic uremia.

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[40] Kolff, W. J.: Serum potassium in uremia, report of 16 cases some with paralysis. J. Lab. & Clin. Med., **36:** 719, 1950.

[41] Kohn, R. M. and Kiley, J. E.: Electrocardiographic changes during hemodialysis, with observations on contribution of electrolyte disturbance to digitalis toxicity. Ann. Int. Med., **39:** 38, 1953.

* Some recent examples of acute uremia treated with the artificial kidney have been presented in the *Transactions of the American Association of Genito-Urinary Surgeons.*[3]

[42] Oliver, J., MacDowell, M. and Tracy, A.: Pathogenesis of acute renal failure associated with traumatic and toxic injury; renal ischemia, nephrotoxic damage and ischemuric episode. J. Clin. Investigation, **30:** 1307, 1951.

[43] Davison, J. C. and McDaniel, W. H.: Anuria following treatment with a multiple sulphonamide preparation. Ulster M. J., **19:** 176, 1950.

3) *Chronic uremia.* Goldner, Gordon and Danzig[44] recently reported some of their results from the use of dialysis in the treatment of patients with chronic renal disease. Of 20 cases of chronic uremia that had been treated carefully before and had shown little improvement, 13 had improvement of their symptoms which lasted an average of three days after dialysis with the artificial kidney. Surprisingly, seven had remissions lasting an average of two months. This corroborates the experience of Alwall[18] in Sweden and ours.*

4) *Intoxications without primary nephrotoxic actions.* Some intoxications may be treated with the artificial kidney to remove the poison by dialysis. Bromide[45, 46] is more effectively removed by the artificial kidney than by the human kidneys. Salicylates are well removed by dialysis.[47, 48] Of the barbiturates,[49-51] some are dialyzable[51a] (phenobarbital (luminal)), some are slightly dialyzable (pentobarbital (nembutal)), but others are almost undialyzable[51a] while bound to plasma proteins (secobarbital (seconal) and amybarbital (amytal)).

5) *Dialysis as pre- or postoperative measure.* Hemodialysis is occasionally of value in preparing a patient with uremia for surgery,[39] especially if the objective of the operation is removal of the cause of the urinary suppression.

6) *Intractable edema as indication for treatment.* Intractable edema may occur in many clinical conditions and often complicates acute or chronic uremia. Skeggs, Leonards and Heisler's artificial kidney used as dialyzer-ultrafilter[52] can remove 1000 to 1200 ml. of ultrafiltrate from a patient per hour.[3, 52a] Other types of filtrating and dialyzing kidneys are less effective, but can be used.[53] Hematocrit determinations must be done during treatment to recognize too

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[44] Goldner, F., Gordon, G. and Danzig, L. E.: Use of artificial kidney in chronic uremia. A.M.A. Arch. Int. Med., 93: 61, 1954.

[*] Several reports of patients who had chronic uremia and were followed for several months or a year after dialysis (peritoneal lavage) have been published elsewhere.[10]

[45] Merrill, J. P. and Weller, J. M.: Treatment of bromism with artificial kidney. Ann. Int. Med., 37: 186, 1952.

[46] Wolf, A. V.: Artificial kidney. Science, 115: 193, 1952.

[47] Bywaters, E. G. L. and Joekes, A. M.: Artificial kidney; its clinical application in treatment of traumatic anuria. Proc. Roy. Soc. Med., 41: 420, 1948.

[48] Doolan, P. D., Walsh, W. P., Kyle, L. H. and Wishinsky, H.: Acetylsalicylic acid intoxication, a proposed method of treatment. J.A.M.A., 146: 105, 1951.

[49] Alwall, N [illegible] artificial kidney XX. Treatment of [illegible] forced polyuria, exchange ultrafiltra- [illegible] treatment of barbiturate poison- [illegible]

[illegible] H., Walsh, W. P., Doolan, P. D., Wishinsky, H. and Pallotta, [illegible] Application of hemodialysis to treatment of barbiturate poisoning. J. Clin. Investigation, 32: 364, 1953.

[51] Walsh, W. P., Kyle, L. H., Doolan, P. D. and Jeghers, H. J.: Treatment of barbiturate poisoning by hemodialysis. Am. J. Med., 13: 104, 1952.

[51a] Leonards [illegible] Removal of barbiturates from blood by artificial kidney. Fed [illegible]

[52] Leonar [illegible] rmal and edematous dogs by [illegible]

[52a] Kolff, W. J. an [illegible] dialysis or filtration. Cleveland Clin. Quart. 21: 61, 1954.

[53] Lunderquist, A. (in collaboration with Alwall, N. and Torr [illegible] kidney XXI. Efficacy of the dialyser—ultrafilter intended for h [illegible] liminary report on treatment oedemic patients by means of [illegible] Scandinav., 143: 307, 1952.

rapid dehydrations. During the ultrafiltration we find it useful to maintain the circulating plasma volume with dextran.

Since some oliguria may follow treatment with ultrafiltration, it is necessary to restrict the patient's fluid intake the following days. Sometimes diuresis follows a single treatment with a filtrating-dialyzing artificial kidney.[3, 52a]

The purely dialyzing, nonfiltering types of artificial kidneys are less effective in removing edema, but by the addition of extra glucose to the rinsing fluid (1½ to 5 per cent) considerable amounts of fluid may be removed.[54, 52a] In this way Lewis and others[55] induced a weight loss of 4 kg. in 6 hours of dialysis. However, these authors and Merrill et al.[31] gained the impression that high concentrations of glucose caused vomiting and drowsiness of the patient. This concurs with our experience. Blood sugar content may rise over 700 mg. per hundred ml., necessitating the use (10–40 u. per hour) of insulin intravenously.

CONTRA-INDICATIONS FOR TREATMENT WITH THE ARTIFICIAL KIDNEY

Active uncontrollable bleeding is the only absolute contra-indication to treatment with the artificial kidney. Heparinization may activate gastro-intestinal hemorrhages, often present in severe uremia,[56] but this is rarely serious. The ulcerations found in the rectum of patients with bichloride of mercury poisoning may bleed under the influence of heparinization. Wounds not bleeding before dialysis present a calculated risk.

SUMMARY

"Conservative" management suffices for the majority of patients with acute urinary suppression. When it does not, the dialyzing methods (artificial kidneys, peritoneal and intestinal lavage) are valuable adjuncts. Dialysis is also useful in the treatment of certain cases of chronic uremia, for the removal of some poisons, and for the removal of otherwise intractable edema. By the use of plastic tubing and silicone-coated glassware in artificial kidneys, little heparin is required; consequently, danger from hemorrhage is minimized. Among the dialyzing methods, the rotating artificial kidney is the most effective in terms of clearance. Among the artificial kidneys that use dialysis and filtration, the one of Skeggs, Leonards and Heisler is most effective in terms of clearance, and it can also be used as an effective ultrafilter.

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[54] van den Bossche, M. and Kolff, W. J.: Possible removal of edemic fluids by dialysis with hypertonic glucose solution. Geneesk. gids, 26: 284, 1948.

[55] Lewis, F. J., Reiser, M. P., Egdahl, R. H., Raffucci, F. L. and Flink, E. B.: Clinical uses of artificial kidney. Journal-Lancet 72: 1, 1952.

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SUCCESSFUL USE OF SIMPLIFIED METHOD OF INTERMITTENT PERITONEAL DIALYSIS

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Since its introduction by Ganter[1] in 1923, peritoneal dialysis has been a controversial means of treating human renal insufficiency Due to the impetus of Frank, Seligman and Fine's[2] re-introduction of peritoneal lavage in 1946, peritoneal dialysis was employed rather widely for several years Despite a modification of their method, Frank and co-workers[3] noted a high incidence of peritonitis and advised that dialysis be stopped after a maximal period of 72 hours in order to lessen this hazard. By 1951, peritoneal dialysis had been generally abandoned as a means of therapy for severe uremia because of mechanical difficulties which may prevent adequate drainage of the peritoneum, because of difficulties encountered in controlling water and electrolyte balance, and because of the risk of fatal peritonitis [4]

In 1951, Grollman, Turner and McLean[5] described a twice daily technique of peritoneal lavage which they successfully used in nephrectomized dogs for periods up to 70 days without the development of infection They applied their technique to five human cases, but employed peritoneal dialysis at 2 hour intervals for a total duration of 16 to 48 hours They failed to demonstrate that peritoneal dialysis can be applied to the human for extended periods without the development of peritonitis

Recently, Legrain and Merrill[6] reported a simplified technique of short-term continuous peritoneal dialysis which is advisedly not repeated in less than 48 hours because of an increasing risk of infection with a greater duration of dialysis

It thus appears that peritoneal lavage for extended periods of time has not proven itself without considerable clinical hazard

This paper describes the successful clinical use of intermittent peritoneal dialysis in a simplified and interrupted fashion for 29 days Since adequate drainage of the irrigating fluid and control of fluid and electrolyte balance were also demonstrated, the thesis is presented that intermittent peritoneal lavage can be performed in the human for extended periods of time without the development of peritonitis or other serious complications The value of this simplified method of intermittent peritoneal dialysis in the relief of severe potassium intoxication is demonstrated in a second case

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[1] Ganter, G Munchen med Wchnschr 70: 1478, 1923

[2] Frank [illegible]

[3] Fran [illegible]
Rutenbu [illegible]

[4] Kolff [illegible] 1951

[5] Grollman, A , Turner, L B and McLean J A Arch Int Med , 87: 379-390, 1951

[6] Legrain, M and Merrill, J P New Eng J Med , 248: 125-129, 1953

MATERIALS AND METHODS

The technique of intermittent peritoneal dialysis employed is a modification of the method of Grollman, Turner and McLean.[5]

The basic lavage fluid consists of lactated Ringer's solution, U.S.P. or in the case of severe potassium intoxication, a solution made by mixing two parts by volume of 0.9 per cent sodium chloride (e.g. isotonic sodium chloride solution, U.S.P.) and one part by volume of sixth-molar racemic sodium lactate solution (e.g. sodium lactate injection, 1/6 molar, U.S.P.). The electrolyte composition of the perfusion fluid is described in table 1. To the basic lavage fluid, glucose is added to a final concentration of 2 to 6 gm. per 100 ml. in order to obtain the desired osmolarity of the perfusion fluid. For this purpose, 50 ml. ampules of 50 per cent glucose solution are used. Penicillin (50,000 units) and streptomycin (0.5 gm.) are added to each liter of fluid. All of the materials used in the lavage fluid are generally available and may be purchased in a sterile form for clinical use.

A routine abdominal paracentesis set is employed and, with aseptic precautions, a typical paracentesis is performed in the median line below the umbilicus of the patient. With the patient supine, the stylet is removed and tubing from an intravenous infusion set is attached to the proximal end of the trocar. The lavage fluid, preferably warmed to body temperature, is instilled during a brief period to a total volume of 3 to 3.5 liters. The trocar is then withdrawn.

A rounded tack-like rubber cap found on the needle adapter part of an infusion set (Amiset, Mead Johnson and Co.) is used as a plug and the stem of the plug is inserted into the superficial part of the paracentesic opening. The stem of this plug or cap has an external diameter of 0.6 cm. and both its length and the diameter of the top of the plug are approximately 1.2 cm. Over the plug, a sterile pressure dressing with a scultetus binder is applied.

Within 2 to 4 hours, or in 4 to 6 hours in the case of severe hyperpotassemia, the patient is placed in a sitting position and the dressing and plug are removed. Then, the trocar is re-inserted at the same site without anesthesia and paracentesic drainage is accomplished by gravity. The site is then redressed.

Such a technique of peritoneal dialysis is repeated as necessary, even two or three times daily.

TABLE 1. *Electrolyte composition of fluid for peritoneal dialysis*

Ions, mEq./L.*	Lactated Ringer's Solution, U.S.P.	Lactated NaCl Solution
Na^+	130	158
K^+	4	
Ca^{++}	3.5	
Cl^-	109.5	103
$C_3H_5O_3^-$	28	55
mOsm./L.†	275	316

* Before addition of 50% glucose.

† Total milliosmolarity.

I. INTERMITTENT PERITONEAL LAVAGE THERAPY DURING PROTRACTED ANURIA

Observations. A 14-year old boy entered the hospital on April 9, 1951 because of a petechial eruption of 2 weeks' duration. Physical examination revealed generalized petechiae and slight peri-orbital edema. Laboratory examination showed signs of acute glomerulonephritis with azotemia. The patient gradually became oliguric.

The patient's serum electrolyte concentrations during hospitalization are chronologically recorded in figure 1.

Generalized clonic convulsions developed. On April 28, the patient was disoriented, amaurotic, and very lethargic. *The seizures, not prevented by intravenous* calcium administration, were becoming more frequent. Virtual anuria ensued and persisted, with urinary volumes ranging from 0 to 50 ml. per day and rarely exceeding 5 ml. per day.

Observations and results during peritoneal dialysis. In the evening of April 28, 1775 ml. of lactated Ringer's solution, U.S.P., modified with glucose and antibiotic, were introduced intraperitoneally through tubing attached to an 18 gauge spinal puncture needle. Later, a paracentesis was attempted unsuccessfully (the trocar was not introduced sufficiently deep).

The next day, 2300 ml. of the lavage solution were instilled intraperitoneally. Three and one half hours later, by paracentesic drainage, 3,400 ml. of fluid were obtained. Then, 3,450 ml. of the lavage solution were instilled through the same abdominal trocar. Five and one half hours later, a trocar was re-inserted and 3,400 ml. of fluid were again obtained.

The following day, a volume of 4,600 ml. of fluid was instilled and a pres-

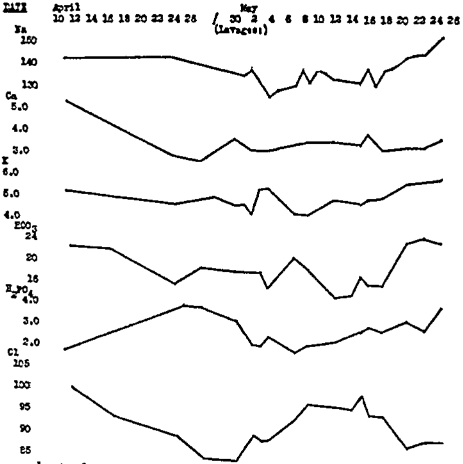

FIG. 1 Serum electrolytes before and during peritoneal lavage therapy in mEq/L; phosphate in mmoles/L.

Postmortem observation. Grossly, the peritoneum was everywhere within normal limits, save for a few small fibrous adhesions of the parietal peritoneum immediately adjacent to the site of the paracenteses. Many sections of intestine were examined microscopically and the serosa and subserosa of the intestines were entirely within normal limits. Edema, however, of the subserosa of the gallbladder was observed.

Lesions of a necrotizing panarteritis were found in the heart, adrenals and kidney in association with a severe diffuse glomerulosclerosis. Apparently, the patient died from myocardial failure due to myocardial infarction, the result of a hypersensitivity angiitis.

II. INTERMITTENT PERITONEAL LAVAGE THERAPY FOR ACUTE POTASSIUM INTOXICATION

Intermittent peritoneal dialysis was also used to relieve severe potassium intoxication in a case of acute anuria due to glomerulonephritis.

Materials and methods. The technique employed was identical with the method previously described except for the nature of the lavage fluid. Lactated Ringer's solution, U.S.P., was avoided because of its potassium content of 4 mEq/L. Instead, a solution of sodium chloride and racemic sodium lactate was utilized with glucose added to a 4.4 gm. per cent concentration.

Observations and results. A 25-year old housewife was hospitalized on February 4, 1952 with increasing weakness, dyspnea and mild hemoptysis. The patient had had a chronic productive cough. Physical examination revealed slight peri-orbital edema and sonorous musical rales bilaterally. Laboratory examination showed signs of acute glomerulonephritis with azotemia.

Ten days after admission, the patient became anuric and more dyspneic. The blood urea level was now 376 mg. per cent and the serum potassium 7.7 mEq/L. An electrocardiogram showed evidences of potassium intoxication.

Despite the slow intravenous administration of 87.5 gm. of glucose with 25 units of insulin, the patient failed to manifest significant clinical improvement. The subsequent blood urea level was 569 mg. per cent and the serum potassium value was 8.1 mEq/L. In a few hours, an electrocardiogram revealed signs of intense potassium intoxication with almost complete disappearance of P waves, atrial-ventricular dissociation, and complete right bundle branch block (fig. 2, *A*).

Peritoneal dialysis with 3.4 liters of the lactated sodium chloride-glucose solution was performed for four hours. During this dialysis, the cardiac rhythm became regular and the patient improved clinically. An electrocardiogram (fig. 2, *B*) taken immediately after the dialysis showed practically normal findings in contrast to the severe potassium intoxication of the heart previously present.

In a few hours, however, the patient became more dyspneic and electrocardiographic signs of severe hyperpotassemia re-appeared. Two more intermittent peritoneal lavages were successfully performed. The patient became extremely dyspneic and cyanotic and expired on her twelfth hospital day.

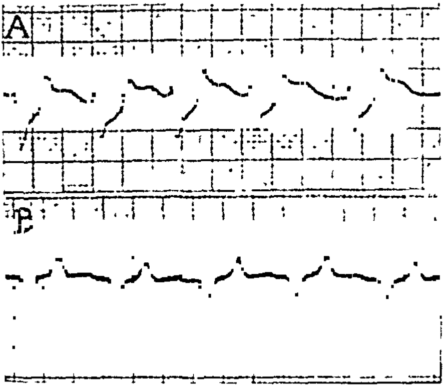

FIG. 2 Electrocardiograms (lead 1) showing *A*, intense potassium intoxication immediately before dialysis and *B*, marked improvement after 4 hours of peritoneal dialysis with lactated sodium chloride-glucose solution

Postmortem examination revealed massive intrapulmonary hemorrhage, tubular bronchiectasia, and extensive acute and subacute glomerulonephritis.

DISCUSSION

Lactated Ringer's solution, U.S.P., having a decreased sodium: chloride ratio when compared with normal plasma, has a tendency to reduce the plasma carbon dioxide combining power. Although its lower sodium concentration (130 mEq/L) than that of normal plasma is advantageous in the presence of edema, cardiac failure, or severe hypertension, sodium bicarbonate or lactate may occasionally be desirable supplemental therapy by mouth or by vein.

During the 29 days of peritoneal dialysis described above, frequent aerobic and anaerobic cultures of the lavage fluid were attempted and, in every instance, no growth was found. Upon postmortem study, gross and microscopic signs of peritonitis were absent despite 45 intermittent peritoneal dialyses over the 29 day period. It thus appears that peritonitis is not inevitable with all forms of peritoneal dialysis performed for an extended period. Intermittent lavage, up to two or three times daily, is recommended to avoid the high incidence of peritonitis previously found in clinical studies. The caution of Legrain and Merrill[6] not to repeat peritoneal dialysis within 48 hours appears inapplicable if the method of intermittent lavage is utilized interruptedly even as often as several times a day.

The demonstration that fluid and electrolyte balance were controlled, drainage of the irrigating fluid was adequate, and peritonitis was absent during intermittent peritoneal dialysis in the human for 29 days affords strong evidence against generally abandoning this means of treating severe renal failure.

For the alleviation of potassium intoxication if severe despite conservative therapy, intermittent peritoneal dialysis is advocated employing a lactated sodium chloride solution. Sufficient glucose should be added to make the lavage solution somewhat hypertonic to the patient's plasma. Besides removing sizable amounts of potassium, this dialyzing fluid may also lessen the toxicity of the hyperkalemia due to its excess amount of sodium ion. Tabor and Rosenthal[7] demonstrated the toxicity of potassium administered in solutions devoid of sodium.

Clinically, intermittent peritoneal dialysis should prove most useful as an adjunct to the conservative treatment of renal insufficiency. Although intestinal lavage, such as the method of Hicks and associates,[8] is an effective means of removing potassium, the fluid and electrolyte distribution during intestinal lavage is difficult to control.[9]

When vividialysis is necessary for the alleviation of severe hyperpotassemia or serious uremia, hemodialysis by means of an artificial kidney or peritoneal dialysis should be undertaken.[9] If bleeding tendencies exist, peritoneal dialysis usually takes precedence over the use of the artificial kidney.[4]

The artificial kidney is a tedious and complex technique. It demands a team of workers for successful use and is not readily available. The simplified technique of intermittent peritoneal dialysis herein described demands less apparatus, less fluid volume, and less attendance. It may be performed as a bedside procedure. Furthermore, the basic irrigating fluid is conveniently prepared from commercially available materials. Grollman[10] has described an irrigating fluid made from commerically available solutions and from magnesium chloride.

The method of intermittent peritoneal dialysis is simpler and appears to have more advantages than the continuous technique of Legrain and Merrill.[6] They recommend the use of an irrigating solution which is not commercially available and constant attention must be paid to the maintenance of proper balance between inflow and outflow tracts for an average duration of 12 to 15 hours. With Legrain and Merrill's method, the average extraction ratio of potassium is about 30 per cent with a rate of flow of two liters per hour.[6] In the experience of the author, the extraction ratio per unit volume is approximately 66 per cent for both potassium and inorganic phosphate and is about 100 per cent for urea* when intermittent dialysis is employed for 4 hours. Furthermore, less fluid volume is used in the interrupted or intermittent method of dialysis over a 48 hour period than in the continuous method of peritoneal lavage.

In 1951 Kolff[11] stated that death from acute uremia should be extremely rare. If Kolff's opinion is to become a realization in the near future, the more practical availability of a simplified form of intermittent peritoneal dialysis appears to be a crucial factor.

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[8] Hicks, M. H., Grutchfield, A. J. and Wood, Jr. J. E.: Am. J. Med., **9**: 57–62, 1950.

[9] Corcoran, A. C.: J.A.M.A., **153**: 1233–1236, 1953.

[10] Grollman, A.: Acute Renal Failure: Springfield, Charles C Thomas, 1954, pp. 62–64.

* The extraction ratio of urea is frequently higher than 100 per cent. This paradox has been also observed and explained by Grollman, Turner and McLean.[5]

[11] Kolff, W. J.: Clev. Clin. Quart., **18**: 216–228, 1951.

SUMMARY AND CONCLUSIONS

A simplified method of intermittent peritoneal dialysis is described. It may be conveniently carried out as a bedside procedure utilizing readily available materials.

With the long-term frequent use of intermittent peritoneal lavages in the human, control of fluid and electrolyte balance, adequate drainage, and an absence of bacterial peritonitis are obtainable.

This technique of intermittent peritoneal dialysis should prove a valuable adjunct to the conservative treatment of acute potassium intoxication or severe uremia.

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STUDY AND MANAGEMENT OF UROLOGICAL PATIENTS WITH RENAL FAILURE

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Renal insufficiency seen in a urological service is typically the result of obstruction and/or infection. Even after the obstacle to urinary flow has been removed and the infection cleared, the patient may be left with transient or permanent renal inadequacy. The following account describes our management of changes resulting from markedly subnormal renal function in urological patients who are about to undergo surgery, who have undergone surgery, or in whom surgery was considered to be contra-indicated.

The operations, incidentally mentioned, were performed by several members of the attending and resident staff. Details of these procedures are not given as they are immaterial in the present report. Thanks are extended to the following members, past and present, of the Columbia-Presbyterian Medical Center for light and stimulation on various aspects of this study: Stanley E. Bradley, Charles L. Fox, Jr., David V. Habif, Gilbert H. Mudge and Kermit L. Pines.

A. RENAL FAILURE FROM INFECTION AND MULTIPLE OR LARGE PELVIO-CALYCEAL STONES

Case 1. (PH 770102.) In 1952 a 70-year-old white woman was admitted because of bilateral staghorn calculi that had been present at least since 1937. She was first seen in 1945 with large dendritic calculi with satellites in both kidneys and bilateral hydronephrosis. The $[\text{inorg. P}]_s$,* $[\text{Ca}]_s$,* blood urea nitrogen, and $[\text{alkaline phosphatase}]_s$* were normal but she was moderately anemic. The urine was alkaline with microscopic hematuria and was free of bacteria. Her blood pressure was 200/100 and she had tenderness to deep palpation in the right renal region. In 1945 treatment was not specific. Nephrolithotomy was not performed because of her borderline renal and cardiac status. She was lost to follow-up until 1947, at which time there was no change in the renal calculi; the $[\text{Ca}]_s$ and $[\text{inorg. P}]_s$ were normal but the blood urea nitrogen had risen to 25 mg./100 cc. Urine culture showed Staphylococcus albus. Recurrent gross hematuria and pain in the renal regions continued. She was treated thus: 1) "maintenance calcium" diet, i.e. about 600 mg. daily;† 2) neutral or slightly acid-ash diet; 3) Al(OH)_3 suspension (4 per cent) with Mg trisilicate (12.5 per cent), 30 cc 4i.d. to reduce the absorption of phosphorus through the intestinal tract; 4) FeSO_4 150 mg. t.i.d.; 5) analgesic for pain.

In 1948 she was digitalized and put on a low NaCl diet because of her moder-

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* Abbreviations or names of chemical elements or compounds within brackets indicate concentration. Subscript s indicates concentration in serum.

† "Daily" implies "in 24 hours."

ately advanced arteriosclerotic heart disease. Two years of steady Al(OH$_3$) produced no effect on her [Ca]$_s$ or [alkaline phosphatase]$_s$ although moderate osseous demineralization had developed within a year. In 1919 there was no radiographic change in her renal calculi. She was continued on the above regimen. In 1951 a stubborn Bacillus proteus infection developed in her urine for which she was given mandelic acid 2 gm. q.i.d. for 14 days. Her blood urea nitrogen was 41 mg./100 cc, [HCO$_3$]$_s$ 19.8 mEq/L, and [Cl]$_s$ 112 mEq/L. She was continued on an acid-ash diet and requested to drink at least 3 liters of water daily. In December 1951 her [alk. phosphatase]$_s$, [inorg. P]$_s$, [Ca]$_s$, [Na]$_s$, and [K]$_s$ were normal. Her [creatinine]$_s$ was 1.75 mg./100 cc; her endogenous creatinine-clearance 22.1 cc/min.; and her blood urea nitrogen 25 mg./100 cc. In spite of the large staghorn calculi, the urinary excretion of Ca and P in 24 hours was only 32.8 mg. and 88 mg. respectively, on one occasion, while on a daily intake of about 150 mg. of Ca. On another occasion the outputs were only 12.9 mg. and 51.2 mg. respectively. In many other cases with staghorn calculi we have also not been able to find hypercalcuria while *the patient was on 150 mg. of Ca daily.*

Early in 1952 she died at home probably from arteriosclerotic myocardial failure, judging from the outpatient electrocardiograms taken shortly before.

Case 2. (PH 036345.) In 1951 an obese 51-year-old Negress had pain in the right renal region for 2 years, blood pressure 140/85, weight 103 kg., afebrile, tenderness 2 plus in right renal region; no tenderness in left. She had a large dendritic staghorn calculus in a relatively small right kidney; neither kidney concentrated diodrast *sufficiently for pyelography, left renal pelvis and calyces* appeared normal by retrograde pyelography; urine had fixed specific gravity, acid reaction and contained B. proteus. Hemoglobin 9.1 gm./100 cc. She was not considered a candidate for nephrolithotomy because of advanced, apparently irreversible, renal failure.

Plasma electrolytes

Base		*Acid*	
Na^+	147.1 mEq/L	Cl^-	106 mEq/L
K^+	4.8	HCO_3^-	9.9
Ca	7.6 mg./100 cc	Pr^-	16.5
		Inorg. P	6.7 mg./100 cc

She habitually drank water copiously and excreted about 3 liters of urine daily. In spite of the large urinary output her blood urea nitrogen remained elevated and essentially stable: an indication of advanced renal damage. On a regular diet, however, *the daily urinary excretion* of K was as expected. Her 2-hour phenolsulfonphthalein excretion was only a trace. To correct acidosis and promote diuresis she was discharged on 90 mEq of Na acetate t.i.d. orally.* To prevent tetany from inevitable drop in the ionized calcium occurring with decreasing acidosis, she was given *5 gm.* of calcium lactate twice daily.† Three months later, as an out-patient, her laboratory data were as follows: [Ca]$_s$ 9.9

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* Sodium acetate therapy is discussed in Commentary.

† See Commentary on use of calcium lactate

mg./100 cc, [inorg. P]$_s$ 3.85 mg./100 cc, [HCO$_3$]$_s$ 15.9 mEq/L, [Cl]$_s$ 119 mEq/L; blood urea nitrogen 83 mg./100 cc; hemoglobin 8.8 gm./100 cc. Her [Ca]$_s$ was normal but she was still in marked acidosis although she "got around", felt well, and lost no weight (fig. 1).

Late in 1952, when last seen by the writer, her renal status (blood urea nitrogen, creatinine, phenolsulfonphthalein) was unchanged; she had continued on 90 mEq of Na acetate t.i.d. and Ca lactate. Her acidosis was somewhat diminished ([HCO$_3$]$_s$ 19.7 mEq/L); her [Ca]$_s$ of 8.5 mg./100 cc and [inorg. P]$_s$ of 5.3 mg./100 cc indicated appreciable retention of phosphate. Her endogenous creatinine-clearance was 14.4 cc/min (about 12 per cent of normal), i.e. of the same order as her urea-clearance a year before. She weighed 101 kg. and reported a good appetite. Her basal metabolic rate was normal.

Case 3. (PH 097918.) In 1952 a 46-year-old white woman was seen; since 1942 she had undergone at least five operations on her kidneys elsewhere. These included several procedures for renal calculi and a left nephrectomy. A large dendritic calculus with satellites occupied her solitary right kidney. She was nauseated and vomited prior to admission. Her blood pressure was fairly stable at 140/90. Her blood urea nitrogen was 115 mg./100 cc; she was acidotic, hypocalcemic, and afebrile.

FIG. 1. Case 2. Pleasant facies and good appetite in spite of a steady blood urea nitrogen exceeding 80 mg./100 cc. Acidosis controlled by Na acetate. Daily urinary output about 3 liters.

The acidosis and hypocalcemia were corrected parenterally promptly as follows:*

Bodily weight = 50 kg.
≡ 30 liters total bodily water.
Actual [HCO$_3$]$_s$ = 7 mEq/L.
Normal [HCO$_3$]$_s$ = 27 mEq/L.
Therefore deficit of HCO$_3$ = (27 − 7) × 30 = 600 mEq.
Now 1,000 cc M/6 Na lactate ≡ 167 mEq lactate or HCO$_3^-$.
Therefore, 600/167 = 3.6 l. M/6 lactate.
Extracellular water (ECW) = 50 kg. × 20/100 = 10 liters.
Actual [Ca]$_s$ = 7.5 mg./100 cc.
Normal [Ca]$_s$ = 9.6 mg./100 cc.
Therefore deficit of Ca = (9.5 − 7.5) × 10 = 200 mg.
[K]$_s$ = 3 6 mEq/L.

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* See Commentary for data on water and electrolyte compartments used in these calculations.

Therefore, therapy today and again tomorrow:

2 liters M/6 Na lactate + 100 gm. glucose.
0.5 liters Mudge's solution.*
1.0 liter 5 per cent dextrose in water.
Ca gluconate 4 gm. i.m. (= 89 mg. Ca × 4; = 356 mg. Ca).

At least 100 gm. of glucose (dextrose) should be given a day to keep ketogenic acidosis at a minimum and to reduce cellular breakdown and protein-loss; the maximum of this effect is obtained by giving 100 gm. glucose daily (Gamble, 1949). This is discussed in the Commentary.

On the second day of parenteral therapy calcium gluconate was omitted and the patient underwent tremors while receiving the sodium lactate intravenously. The tremors ceased shortly after intramuscular injection of 4 gm. Ca gluconate. After two days of parenteral therapy, as outlined above, the $[HCO_3]_s$ rose to 27 mEq/L and the blood urea nitrogen fell to 83 mg./100 cc. On the seventh day after admission the patient was able to take all nourishment orally. At that time her blood urea nitrogen was at a stable minimum of 39 mg./100 cc. Her endogenous creatinine-clearance was 10.7 cc/min. Acidosis was maintained at an acceptable level by 30 mEq Na acetate and 10 mEq K acetate 4.i.d. supported by 2 gm. calcium lactate t.i.d. (fig. 2). To replenish a presumed deficiency of K, indicated by a $[K]_s$ of 3.0 mEq/L, the K acetate was supplemented by 0.3 gm. enteric coated KCl t.i.d. (= 12 mEq). K-supplement was, however, cancelled after the $[K]_s$ rose to 5.3 mEq/L on the eighth day of K-therapy. Several days before discharge it was noted that her acidosis almost could be prevented by raising the Na acetate dosage to 60 mEq 4.i.d.

On a daily Ca-intake of about 150 mg. her 24-hour urinary calcium was 133 mg. and phosphorus 211 mg. During these measurements she excreted 3,250 cc urine and her endogenous creatinine-clearance was 12 cc/min. Her anemia (Hb = 9 gm./100 cc) was corrected by 1,000 cc of blood. To study the size of the spleen before and after transfusion, in an attempt to throw light on the etiology of anemia in uremia, 50 cc of 25 per cent thorotrast (thorium dioxide) were injected intravenously to make the spleen more radiopaque. Transfusion with 1,000 cc of blood did not alter the size of the spleen detectably, thus contraindicating augmented hemolysis as cause of her anemia.

She was discharged on the following therapy:

1) Maintenance (600 mg.) calcium diet.
2) Na acetate 60 mEq 4.i.d.
3) Calcium lactate 2 gm. t.i.d.
4) At least 3 liters of water daily.

Case 4. (PH 946441), a white man who was 56 when seen in 1952, had tuberculosis of the genito-urinary tract in the early 1930's culminating with right nephrectomy and left cutaneous ureterostomy with indwelling ureteral catheter. Urine cultured on several occasions from the left solitary kidney showed no tuberculosis but E. coli and B. proteus. Attempts to dissolve the calculi in

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* Mudge's solution: NaCl 100 mEq/L; KCl 40 mEq/L.

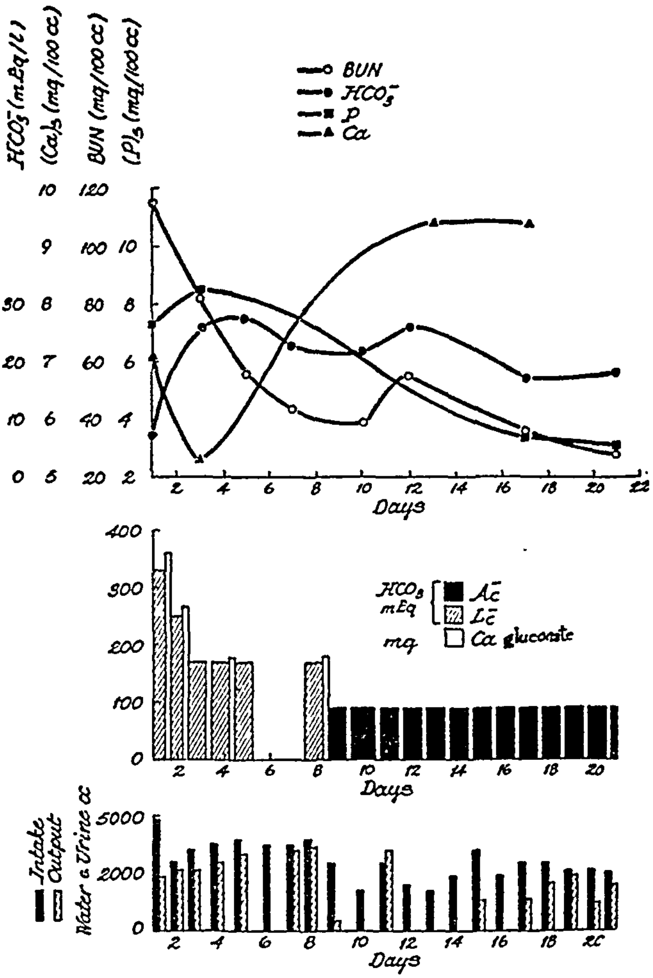

FIG. 2. Case 3. Note correction of $[\mathrm{Ca}]_s$, [inorg. $\mathrm{P}]_s$, BUN, and $[\mathrm{HCO}_3^-]_s$ with parenteral Na lactate and Ca gluconate and then with oral Na acetate.

the pelvis of the left kidney through the ureterostomy catheter by 1½ per cent calsol (ethylene-diamine-tetrasodium acetate) in 1949 produced severe nausea and vomiting and succeeded in decreasing slightly the size and density of the radiopaque stone in the kidney (cf. Gehres and Raymond, 1951).

The patient was re-admitted repeatedly for chills, fever, nausea, vomiting, hematuria, acidosis, and chronic uremia. His blood pressure was 110/60 and his renal function in September 1951 about 15 per cent of normal:

Endogenous creatinine-clearance = 19.6 cc/min.
Renal blood-flow (PAH clearance) = 62 cc/min.*
Glomerular filtration (inulin-clearance) = 12.7 cc/min.*
Filtration-fraction = 20.6 per cent (normal)*

In September 1951 he was put on a Borst diet (high carbohydrate, high fat, low protein) and his blood urea nitrogen fell from 67 mg./100 cc to 45 mg./100 cc; his [creatinine]$_s$, however, remained unchanged at 4.2 to 4.4 mg./100 cc, which indicated no improvement of renal function under such a diet. He was therefore returned to a "maintenance" calcium diet (600 mg.). In 1951 he was discharged on $NaHCO_3$ 2.4 gm. 4.i.d. (= 114 mEq/day) rather than on Na acetate syrup because the latter nauseated him. He also took 2 gm. calcium lactate daily. His renal function, however, continued to diminish and, in September 1952, his endogenous creatinine-clearance was 5.65 to 5.75 cc per minute: approximately half that of the previous year and about 5 per cent of normal. Renal failure was doubtless due to his severe chronic *pyelonephritis* abetted by the indwelling ureteral catheter. His chart on that admission brought out two important items (fig. 3): 1) the drop in [K]$_s$ upon alkalinization with available Na^+; and 2) the prompt rise in [K]$_s$ upon administering K-supplement of only 30 mEq daily, indicating advanced renal damage.

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* Measurements by Dr. Stanley E. Bradley, Department of Medicine, Columbia-Presbyterian Hospital.

Case 5. (PH 868695), a 49-year-old white woman was first seen in 1947 for bilateral renal calculi of 10 years' duration. Her ureters were dilated and scarred bilaterally and it was not possible to eradicate the mixed urinary flora. Bilateral cutaneous ureterostomy was performed in 1948 by the method of Fish and Stevenson (1949). Postoperatively she underwent frequent febrile spikes and her blood urea nitrogen remained elevated. Urine culture showed B. pyocyaneus and B. pro-

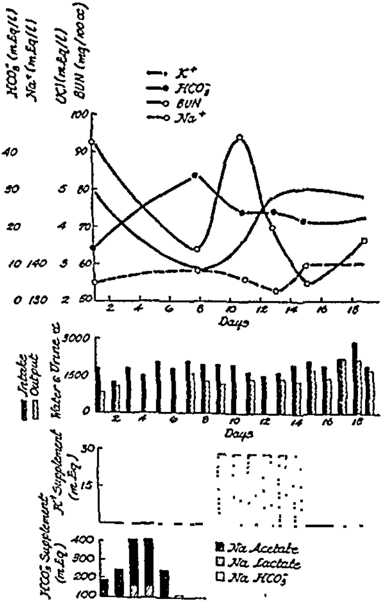

FIG. 3. Case 4. Note drop in [K]$_s$ upon alkalinization with Na lactate and prompt rise in [K]$_s$ upon administering K-supplement orally.

teus. The hydronephrosis augmented. Late in 1950 she underwent left nephroureterectomy because it appeared that her left kidney was not contributing to her well-being but only to a septic course. Acidosis was moderately controlled by 120 mg. Na acetate daily in divided dosage (fig. 4). The pre-nephrectomy blood urea nitrogen was 39 mg./100 cc and the blood urea nitrogen upon discharge about 6 weeks later was 49 mg./100 cc.

Case 6. (PH 022924.) In 1951 a 60-year-old white man had had bilateral renal calculi for 15 years. In 1934 he underwent right nephrolithotomy elsewhere but a calculus remained; in 1938 he underwent nephrolithotomy elsewhere. The calculi recurred. By 1945 he had a right "permanent" nephrostomy and a poorly functioning left kidney. He was followed in another hospital where his nephrostomy tube was changed every 2 months and the tube irrigated in situ with Suby's solution G.

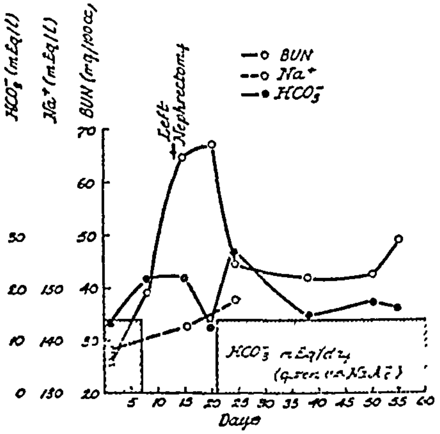

FIG. 4. Case 5. Fall in blood urea nitrogen coincident with administration of Na acetate orally.

Upon his first admission to the hospital, in 1951, his blood pressure was 130/90 and there were large staghorn calculi with satellites in both kidneys. In 1950 an attempt was made to dissolve the calculi in the right kidney by irrigation with calsol through the nephrostomy tube (cf. Gehres and Raymond, 1951). Even after 96 hours of calsol irrigation (2 hours of calsol alternating with 2 hours of isotonic NaCl) no benefit was noted radiographically. The patient's acidosis could be relieved by 120 mEq Na acetate orally daily in divided dosage. His blood urea nitrogen simultaneously descended (fig. 4). Supplying available Na set up a diuresis such that the urinary output exceeded the intake for several days (fig. 5). The fall in $[K]_s$ upon alkalization of the patient without supplying K-supplement should be noted (fig. 4). The blood urea nitrogen remained elevated in spite of a large urinary output, indicating advanced renal failure.

He was re-admitted in July 1951 with nausea, vomiting, weakness, and pain in the left flank. He had been on 120 mEq Na acetate daily but could not tolerate this during the preceding 10 days. On admission the blood urea nitrogen was 106 mg./100 cc, $[Na]_s$ 119 mEq/L, $[K]_s$ 8.3 mEq/L (not available until the following day), $[Cl]_s$ 110 mEq/L, and $(HCO_3)_s$ 9 mEq/L, Hb 7.3 gm./100 cc, and his urine alkaline with specific gravity 1.010. The following day he complained of

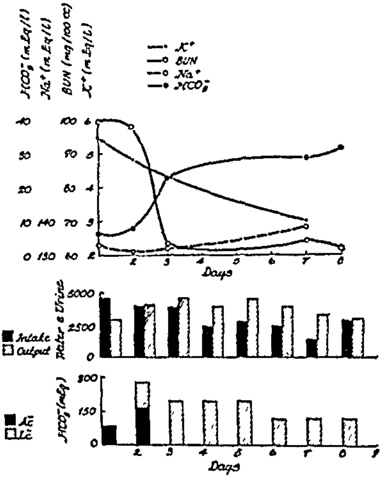

FIG. 5. Case 6. Note fall in blood urea nitrogen and in elevated [K]$_s$ upon alkalinization; also rise in [Na]$_s$.

inability to raise his arms and stated that he was "paralyzed"; he had a bed bath and was unable to move his extremities; his fingers and toes were cold and cyanosed. During the past 24 hours he excreted 1,900 cc of urine. Because of this moderately satisfactory urinary output and his past history of hypokalemia (see fig. 5), it was thought that his weakness might be due to hypo- rather than hyperkalemia. Blood was drawn to confirm this suspicion and he was transfused with 500 cc blood. He died a few hours later. That morning his [Na]$_s$ was 116.5 mEq/L and [K]$_s$ 9.5 mEq/L. These data, however, were available too late to help in averting his death at noon.

Autopsy disclosed normal intracranial contents, thoracic contents, and peritoneal cavity. The pericardial cavity had 25 cc of clear yellowish liquid. The heart weighed 450 gm.; the epicardium was smooth and glistening and the myocardium was not hypertrophied; the coronary arteries were widely patent. His lungs, spleen, liver, adrenals, and gut were normal. The bone marrow and lymph nodes were grossly and microscopically normal. The left kidney was greatly enlarged and appeared little more than a sac full of stones; it had a foul odor and pus; the right kidney had a dilated pelvis and calyces and a markedly thin parenchyma. The parathyroid glands were approximately normal grossly; microscopically they showed hyperplasia of the acidophile and chief cells, presumably secondarily to the chronic advanced renal failure. This case is especially noteworthy because there was hyperkalemia secondarily to extensive renal damage in spite of a daily urinary output of about 2 liters. The patient probably died from ventricular fibrillation and the low [Na]$_s$ at the time may have abetted the fatal hyperkalemia; see the Commentary.

Case 7. (PH 783473.) An obese 62-year-old Negress had had recurrent chills, fever, pain in left flank, and hematuria since 1924. In 1936 she underwent left nephrectomy for calcific pyonephrosis. Postoperatively her blood urea nitrogen was 18.2 mg./100 cc and her right kidney showed blunting of the calyces by excretory urography.

She was followed as an out-patient for intermittent hematuria, pain in the right renal region and cystitis with E. coli. In 1945 it was noted that her right (solitary) kidney had become more hydronephrotic and excretory urography indicated diminished renal function. She was treated by sulfonamides and ureteral dilatation with an 8F ureteral catheter. By September 1950 her blood urea nitrogen rose to 70 mg./100 cc and her $[HCO_3]_s$ was only 9 mEq/L. Her hemoglobin was 8 gm./100 cc and ureteral culture showed B. pyocyaneus; she was thus admitted for re-evaluation. In January 1951 her blood urea nitrogen was 95 mg./100 cc. In March 1951 she was re-hospitalized for dyspnea, orthopnea, and nausea. Her blood pressure was 140/80; blood urea nitrogen 106 mg./100 cc; $[\text{creatinine}]_s$ 12.8 mg./100 cc and her hemoglobin only 6.9 gm./100 cc. Even though the renal calyces showed moderate clubbing, retrograde pyelography disclosed no obstruction along the right pelvi-ureter. It was considered that malfunction of her solitary kidney was due to recurrent pyelonephritis. Our goal was to 1) correct the acidosis, 2) raise the $[\text{calcium}]_s$, 3) maintain normal $[Na]_s$ and $[Cl]_s$, 4) gradually overcome Na-depletion and possible K-loss from the prolonged acidosis and 5) raise the urinary volume to 2–3 liters per diem with ample available base (Na^+) for excretion of acid metabolites (HPO_4^-, $SO_4^=$, organic acids). The method of correction was as already detailed under case 3. Since she was obese her body water was put at 45 per cent of her weight. (See Commentary.) She nevertheless had a stormy course. On Na lactate and Ca gluconate parenterally and, subsequently, Na acetate/K citrate and Ca lactate orally her blood urea nitrogen was reduced to 52 mg./100 cc and her acidosis fully corrected. Her initial hyperphosphatemia of 6.0 mg./100 cc and hypocalcemia of 6.0 mg./100 cc were corrected to normal (fig. 6). She was discharged with a urinary output of 3 liters per day, on Na acetate 30 mEq t.i.d. and Ca lactate 5 gm. daily. She died at home 2 months later.

Failure of this patient's blood urea nitrogen to recede for the first 4 weeks in spite of a daily urinary output of about 2,500 cc indicates marked deterioration of renal function. This was confirmed by her endogenous creatinine clearances of 5.0 to 8.9 cc/min., i.e. 4 to 7 per cent of normal.

B. RENAL FAILURE FROM LONG-STANDING OBSTRUCTION AT THE BLADDER NECK

Case 8. (PH 067435.) A 62-year-old white man presented himself in October 1951 with an indwelling urethral catheter. He had been having severe difficulty in passing his urine and suffered frequent vomiting during the 3 weeks prior to admission. His local physician had found 2,160 cc of residual urine. His blood pressure was 145/90 and hemoglobin 9.3 gm./100 cc; his plasma-protein and electrocardiogram were normal. His skin was dry, scaly, itching, and erupted and his white blood cell differential showed 7 per cent eosinophiles. Obviously

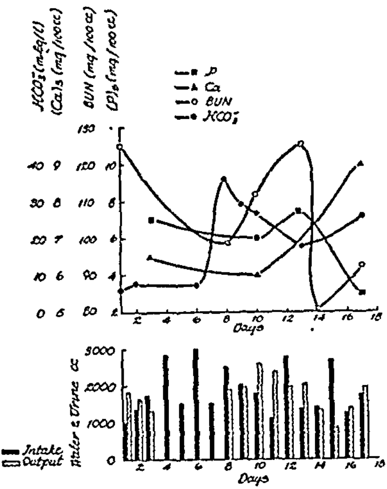

FIG. 6. Case 7. Note correction of $[\mathrm{Ca}]_s$ and $[\mathrm{inorg.\ P}]_s$ to normal by Ca gluconate and correction of acidosis by Na lactate.

he was allergic to one of the antibiotics he had received. His nonprotein nitrogen was 192 mg./100 cc; $[\mathrm{Na}]_s$ 134.8 mEq/L, and $[\mathrm{K}]_s$ 5.9 mEq/L. Bone marrow taken from his iliac crest was essentially normal except for moderate eosinophilia. A suprapubic cystostomy was done.

Nausea and vomiting almost prevented oral nourishment. Fluid intake and dextrose (at least 100 gm. a day) were maintained intravenously and subcutaneously. Although he excreted a large amount of urine daily, his blood urea nitrogen showed no striking decline for over a month, indicating advanced renal damage. This was also emphasised by a tendency to hyperkalemia in spite of the copious urinary output. His $[\mathrm{HCO_3}]_s$, $[\mathrm{Cl}]_s$, $[\mathrm{Na}]_s$ were maintained normal by Na lactate and NaCl parenterally. To reduce twitching and hypocalcemia, calcium gluconate was at times added to the infusions. From time to time he was given a transfusion to maintain his hemoglobin at about 10 gm. During the first month he received 2,000 cc of blood. Nevertheless after about 45 days of such therapy he had edema 3 plus of his extremities and buttocks and became semistuporous. No sign of myocardial failure was apparent and his brachial venous pressure was normal (35–45 mm. water). His edema was explicable by hypoproteinemia. On December 12 his $[\mathrm{protein}]_s$ was 4.8 gm./100 cc; the $[\mathrm{albumin}]_s$ 3.0 gm. and the $[\mathrm{glob.}]_s$ 1.8 gm. He was given 25 gm. of albumin intravenously daily while his venous pressure was being measured as a safeguard; he received protein concentrate (protinol) orally and another 1,000 cc of blood. Within two weeks his $[\mathrm{protein}]_s$ was up to 6.6 gm./100 cc.

During the last three weeks of his hospitalization he received Na acetate 90 mEq daily in a syrup because moderate hyponatremia had developed ($[\mathrm{Na}]_s$

130.0 mEq/L). This syrup, however, contained 30 mEq K as the citrate. After 5 days of this syrup his $[K]_s$ rose to 7.4 mEq/L whereupon the syrup was given without K citrate. Low tolerance to 30 mEq K-supplement orally per diem in spite of copious urinary output was further indication of advanced renal damage.

After about 2½ months of hospitalization he was discharged with a fairly stable nonprotein nitrogen of about 70 mg./100 cc and a suprapubic cystostomy. Several months later his local physician reported that he regularly attended business with the cystostomy tube and that his nonprotein nitrogen was still about 70 mg./100 cc.

Case 9. (PH 103631.) A 71-year-old white man had a chief complaint of urinary incontinence for 6 months, which turned out to be an overflow incontinence. The mass in his lower abdomen was deflated by urethral catheter and yielded over 1,000 cc clear urine. He had a normocytic normochromic anemia (hematocrit 25). Biopsy of his sternal bone marrow indicated diminished erythropoesis, there being a relative decrease in the normoblasts and very few immature forms. There were only 1 per cent megaloblasts; myelopoesis was normal. His $[\text{bilirubin}]_s$ was a mere trace and his urinary excretion of urobilinogen was normal. His fasting blood sugar, electrocardiogram, basal metabolic rate and skull radiograms were normal.

At the time of his admission the patient was ambulatory, ate a regular diet, was rational, and had no complaints other than incontinence. A urethral indwelling catheter was introduced on the tenth post-admission day at which time his blood urea nitrogen was 56 mg./100 cc. During the first day of catheterization the patient became drowsy and remained afebrile. A moderately negative water balance (fig. 7) developed; in the first 5 days his urinary output was 4,800 cc in excess of his water intake; he became hyponatremic ($[Na]_s$ 124 mEq/L) and his blood urea nitrogen rose to 76 mg./100 cc. His blood pressure remained constant at 110/60. On the sixth post-catheter day he became confused. At that time his blood pressure was normal and his weight only 1 kg. below initial. Under urethral catheter drainage his blood urea nitrogen rose irregularly in a month to 137 mg./100 cc at which time his weight was about 5 kg. above the initial and his $[Na]_s$ and $[K]_s$ normal; his $[Cl]_s$ was normal or slightly elevated (fig. 7). Although his urinary output appeared adequate, the steady rise in his blood urea nitrogen without signs of shock suggested that urethral drainage was not satisfactory. A suprapubic cystostomy was done, a 32F mushroom catheter introduced and the urethral catheter removed. Thereafter his blood urea nitrogen steadily fell to slightly above 20 mg./100 cc in 14 days and the tendency to hyperkalemia disappeared (fig. 8). His urinary output nevertheless remained of the same order as prior to suprapubic drainage and his weight remained constant within the limits of error. The fall in blood urea nitrogen thus cannot be explained on a dilution basis. The low $[Ca]_s$ was treated by Ca gluconate as previously described. The hyponatremia was accompanied by disorientation, aggressiveness and vulgarity. Cf. Yannet (1940) for changes in the brain resulting from depletion of extracellular electrolytes. His anemia was treated by 1¼ liters of blood.

On the twelfth post-cystostomy day (fig. 8) he began receiving all fluid and nourishment by syringe through a naso-gastric tube He received 1,200 cc pineapple juice and 1,200 cc skimmed milk daily (both supplying about 70 m/Eq K) in addition to a known quantity of Na acetate. His Na, K, and Cl balance could thus be calculated. Note that [Na]$_s$ failed to rise, in spite of positive balance of Na, until K was given (fig. 8). Thus on the eleventh post-cystostomy day Na-loss in the urine was 106 mEq but the intake was 167 mEq (as Na lactate) and 385 mEq (as NaCl). The patient was in negative Na-balance on September 19 (eighth day in fig. 8), when he received no Na-supplement. When Na was pushed as a readily available ion, i.e. as Na acetate, his Na-balance became positive. His K-balance was strongly positive in spite of a normal [K]$_s$ (fig. 9). This again indicates deficiency of K in the intracellular compartment. His Cl-balance was negative; he lost about 50 mEq of this ion per diem, which is equivalent to a daily loss of 500 cc of extracellular fluid. This paralleled his weight loss.

In spite of a fairly large daily intake of Na, the patient's hyponatremia improved only slowly (fig. 10). As remarked previously, there were indications that the hyponatremia was partly due to entry of Na into the cells secondarily to

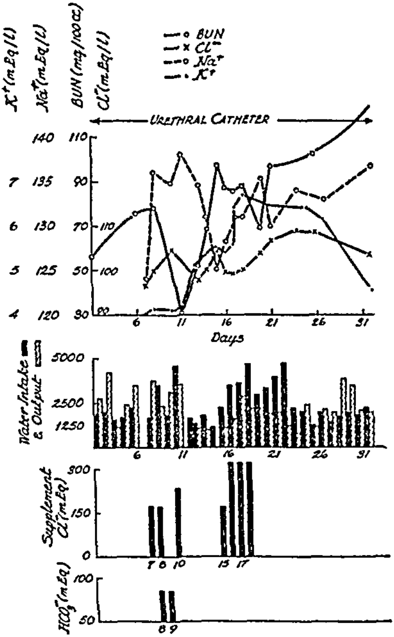

FIG. 7. Case 9. Note moderately negative water balance upon introduction of decompressing urethral catheter; also irregularly rising blood urea nitrogen in spite of urethral catheter and moderate daily urinary output. Also note increasing hyperkalemia, persistent hyponatremia and hypochloremia.

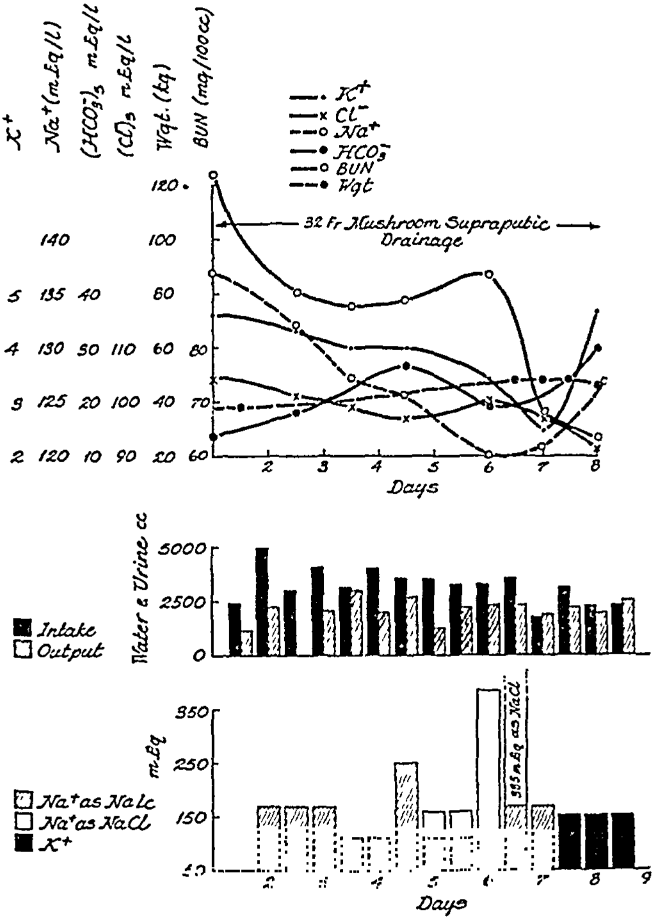

FIG. 8. Case 9 (cont'd). Continuous in time from figure 7 but urethral catheter replaced by wide suprapubic drain. Note steady fall in blood urea nitrogen. Note that $[\text{Na}]_s$ failed to rise, in spite of positive balance of Na, until K was given.

deficiency in intracellular K. The patient's K-intake was thus raised from 70 mEq to 150 mEq/day by introducing K acetate into the naso-gastric tube. Such treatment, however, resulted in prompt rise in the $[\text{K}]_s$ to a dangerous level (fig. 9), necessitating immediate reduction in K-intake. This, together with the immediately preceding strongly positive K-balance, further demonstrates the advanced renal damage of this patient. The hyperkalemia occurred in spite of a daily urinary output of 2,250–2,750 cc. Again, on an adequate intake of available Na (about 250 mEq daily), the patient was in positive Na-balance (fig. 10). He continued, however, in negative Cl-balance while getting 110 mEq or less of Cl daily. At the maximal level of serum K the $\frac{\text{K}}{\text{creatinine}}$ clearance-ratio was 0.6; even at that time, therefore, the patient's tubules were unable to excrete K. Nevertheless tubular excretion of K,* as indicated by a $\frac{\text{K}}{\text{creatinine}}$ clearance-ratio well above unity, has been noted even in chronic renal failure (Platt, 1950).

After several days of Na acetate therapy through the naso-gastric tube the patient's $[Na]_s$ rose to 130 mEq/L, he became rational, and could eat spontaneously. His prostate was enucleated after the second month of hospitalization. His "incontinence" disappeared and he could empty his bladder completely. Two months postoperatively his blood urea nitrogen was 35 mg./100 cc, $[HCO_3]_s$ 23 mEq/L, $[Na]_s$ 134 mEq/L, $[K]_s$ 5 mEq/L, and $[Cl]_s$ 108 mEq/L. He was ambulatory and cerebrated normally.

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* Renal tubular excretion of K was first discovered by McCance and Widdowsen ('37).

Case 10. (PH 071884.) A 71-year-old Negro was seen in December 1951 for advanced carcinoma of the prostate with obstruction and a residual urine of 1,300 cc. His blood urea nitrogen was 110 mg./100 cc, he underwent orchiectomy and was put on stilbestrol; he was discharged, to be followed in the outpatient clinic, with an indwelling urethral catheter, a blood urea nitrogen of 76 mg./100 cc, a normal $[Na]_s$ and $[K]_s$ and an endogenous creatinine-clearance of 8.55 cc/min. (i.e. about 7 per cent of normal). During his hospital stay his acidosis and slightly low $[Na]_s$ were corrected by Na acetate, 120 mEq/day. It was hoped to resect his prostate after his blood urea nitrogen would reach a minimal stable level.

He was re-admitted in August 1952 with extreme pain and tenderness in the

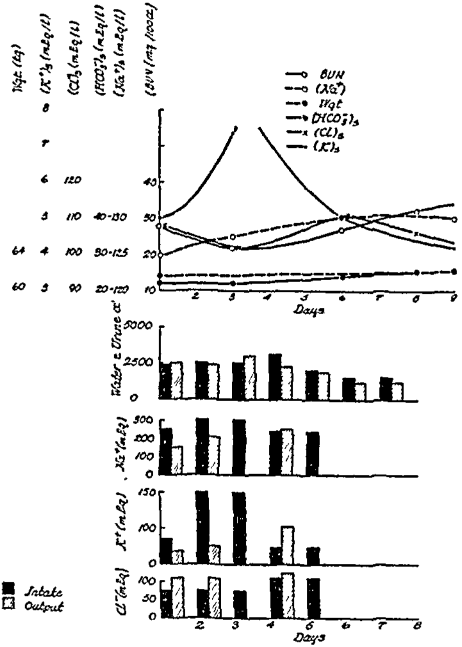
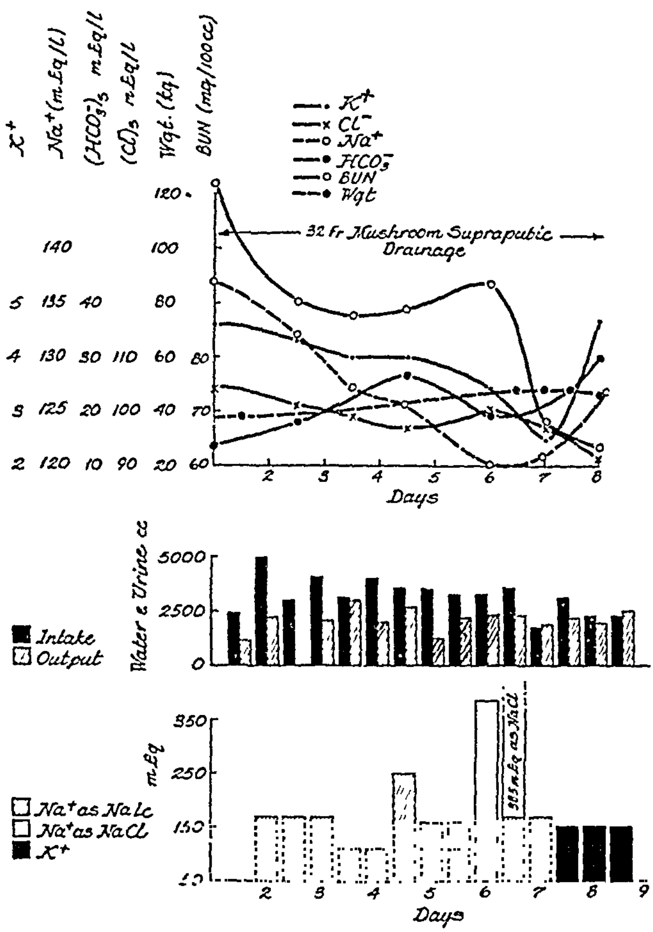


FIG. 9. Case 9 (cont'd). Continuous in time from figure 8. Low $[Na]_s$ is not due to inability to retain Na, because when Na is pushed as a readily available ion, i.e. as Na acetate, Na-balance becomes positive. K-balance positive. Abnormal rise in $[K]_s$ upon increasing the K-supplement by 80 mEq orally and with copious urinary output indicates advanced renal failure.



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After several days of Na acetate therapy through the naso-gastric tube

* Renal tubular excretion of K was first discovered by McCance and Widdowsen (

was performed after the second month of hospitalization at which time his blood urea nitrogen was 43 mg./100 cc. He was maintained indefinitely without a catheter on a regular diet and Na acetate orally (240 m/Eq). His residual urine was less than 10 cc. Four months after admission, when last seen, his blood urea nitrogen was 29 mg./100 cc and his $[Na]_s$, $[K]_s$, $[HCO_3]_s$, and $[Cl]_s$ were essentially normal.

Case 11. (PH 778051.) A 26-year-old white man, seen in 1952 for hyperpiesia (blood pressure 170/90 to 210/125) who, at the age of six, had undergone resection of a congenital obstruction at the internal urethral orifice. In 1940 his blood pressure was 100/70 and in 1945 it was 140/70 to 160/90. He had bilateral hydronephrosis and hydro-ureter, small kidneys, a bladder capacity of 700 cc and residual urine of 65 to 70 cc with a moderate congenital median bar seen cystoscopically and by cystogram. There was bilateral ureteral reflux and a urine culture of E. coli and B. proteus. His hemoglobin was 11 gm., blood urea nitrogen 109 mg./100 cc, $[Na]_s$ 135 mEq/L, $[K]_s$ 4.1 mEq/L, $[Cl]_s$ 98 mEq/L, $[HCO_3]_s$ 15 mEq/L, $[Ca]_s$ 7.0 mg./100 cc, $[\text{inorg. P}]_s$ 11.7 mg./100 cc; and $[\text{creatinine}]_s$ 15.2 mg./100 cc. His endogenous creatinine-clearance was 7.7 cc/min., i.e. about 6 per cent of normal. His urinary output attained 3,600 cc/24 hours without change in the $[\text{creatinine}]_s$, thus indicating advanced renal damage. To test result of bladder drainage, an indwelling 18F balloon urethral catheter was introduced. After about 2 weeks of this his $[\text{creatinine}]_s$ was still 15.2 mg./100 cc although his blood urea nitrogen had fallen to 74 mg./100 cc. The stable, elevated $[\text{creatinine}]_s$ indicated that the patient did not improve by bladder drainage; the fall in blood urea nitrogen was considered to be at least partly due to his low protein diet. The acidosis and somewhat low $[Na]_s$ was completely corrected by Na acetate (240 mEq Na/24 hours); concomitantly he received Ca lactate 7.2 gm./day.

Case 12. (PH 040157.) An 82-year-old white woman was admitted with bladder neck obstruction due to squamous cell metaplasia; hypotonic bladder with diminished sensation; bladder capacity 850 cc; residual urine 700 cc. Blood urea nitrogen 165 mg. per cent, $[HCO_3]_s$ 4.5 mEq/L. The patient was alert and witty although she had spells of nausea and vomiting. She was treated by intravenous M/6 Na lactate; then by $NaHCO_3$ and calcium lactate orally. Her blood urea nitrogen fell to 62 mg. per cent and her $[HCO_3]_s$ was corrected to 19 mEq/L. These corrections occurred while she had an indwelling urethral catheter.

C. UREMIA AND ACIDOSIS FROM MISCELLANEOUS PROTRACTED CAUSES

Case 13. (PH 044719.) A 59-year-old Negress was admitted for fever and pain and tenderness in the right renal region bilaterally. Anamnesis from her son indicated pain, intermittent, in the renal region, bilaterally, for 20 years. For the past 2 months she had intermitted bouts of chills, fever, nausea, and vomiting with pain in one or the other renal region and a weight loss of 10 kg. Her blood pressure was 100/70; she was not obviously dehydrated; she weighed 56 kg. and her respiratory rate was 16/min.; temperature 100F, and pulse 86/min. The pH of her arterial blood was slightly acid (7.25). She had pyuria with Strept.

viridans and Staph. albus. Her blood urea nitrogen was 135 mg./100 cc; $[\text{creatinine}]_s$ 19.8 mg./100 cc; $[\text{Na}]_s$ 132 mEq/L; $[\text{K}]_s$ 5.3 mEq/L; $[\text{Ca}]_s$ 4.1 mg./100 cc; and $[\text{inorg. P}]_s$ 12.3 mg./100 cc. In the first 24 hours she excreted only 700 cc of urine. The electrocardiogram had long Q-T intervals which may have been due to the low $[\text{Ca}]_s$; otherwise the electrocardiogram was normal; her hemoglobin was 7.2 gm./100 cc. Retrograde pyelography showed small obviously contracted kidneys. During hospitalization her urinary output never exceeded 750 cc/24 hours and was usually considerably less. Her daily urinary excretion of K was about a third of that expected from a person receiving over 100 gm. glucose daily (see the Commentary). She was therefore doubtless accumulating K in her extracellular fluid. She was in semi-stupor most of the time until death, probably in hyperkalemia, on the tenth post-admission day.

Autopsy by Dr. Donald King disclosed a right kidney of 50 gm. and a left of 47 gm. The renal surfaces were granular and there was no distinct cortex; there was no obstruction. Much of the renal cortex was replaced by scar; remaining were relatively few scarred glomeruli and tubules with atrophic epithelium; there was abundant infiltration by polymorphonuclears. In summary, her kidneys showed advanced late pyelonephritis probably superimposed on congenitally small kidneys. The adrenal glands were normal, both weighing 12 gm. The gastro-intestinal tract showed no ulceration in the mucosa but there were many congested blood vessels in the submucosa. The spleen and skeleton showed no abnormality; the bone marrow appeared normal; the heart weighed 320 gm. and was normal; the lungs and peritoneal cavity were normal. Essentially the only positive finding was bilateral chronic pyelonephritis with contracted kidneys.

Case 14. (PH 920290.) A 35-year-old white woman was examined in 1952; she was first seen at age 24 in 1939 for pain in the right renal region with weight loss and marked anemia. At that time her hemoglobin was 8.5 gm./100 cc, red blood cells 3 by 10^6/c.mm. with 3.4 per cent reticulocytes; her blood urea nitrogen and blood pressure were normal. There were palpable masses in both flanks and she had frequent bouts of fever. Retrograde pyelography suggested polycystic kidneys. She underwent multiple admissions for re-evaluation and blood transfusions. Hematological study in 1942 showed the following: hemoglobin 8.7 gm./100 cc; red blood cells 3.17 by 10^6/c.mm.; with 2.8 per cent reticulocytes; mean corpuscular diameter 8.0μ; cells normo- to slightly hypochromic; white blood cells and differential normal. Sternal bone marrow biopsy disclosed moderate hyperplasia with hemosiderosis in the large mononuclear phagocytes. This was considered to indicate an increased rate of red blood cell lysis. The reticulocyte response to liver was not impressive.

She continued with frequent febrile episodes and her urine cultured E. coli and Staph. aureus. In 1943 she underwent a right nephrectomy and adrenalectomy which revealed liposarcoma of the kidney (cf. Fish and McLaughlin, 1946). Her blood urea nitrogen upon discharge was 37 mg./100 cc. In 1950 her blood pressure was about 150/90 and other laboratory studies were as follows: hematocrit 34.3 per cent; hemoglobin 10.6 gm./100 cc; red blood cells 3.92 by 10^6/c.mm.; MCV 88c.(normal); MCHC 31.2 gm./100 cc (normal = 33–38);

the patient thus had a normocytic slightly hypochromic anemia. The blood urea nitrogen was 41 mg./100 cc and the [creatinine]$_s$ 2.1 mg./100 cc. She continued to be hospitalized for transfusions. The following table shows the rapid fall in her [Hb] after a transfusion and raises the question of the value of *large* transfusions in such a case:

Date	RBC × 10^6	Hb (gm /100 cc)	Blood Rec'd (cc)
30 Sept. '50	3.6	9.0	
31 Sept.–3 Oct. '50			2,000
4 Oct. '50	4.8	15.1	
8 Jan. '51	3.76	9.4	
11–18 Jan. '51			2,000
18 Jan. '51	4.53	12.5	
23 Feb. '51	3.34	10.7	
30 Mar. '51	3.35	9.2	
4 May '51	3.07	9.2	

In May 1952 a further investigation was made into the etiology of her anemia. The laboratory tests were as follows: stool for guaiac negative; gastro-intestinal series negative; urine culture: no growth; [bilirubin]$_s$ trace; direct Coombs' test negative; fecal urobilinogen 330 mg./100 gm. and 135 mg./100 gm.; urinary urobilinogen: trace. In June 1952 she expired in cachexia, anemia (hemoglobin 3.8 gm./100 cc), and uremia (blood urea nitrogen 150 mg./100 cc). Autopsy showed peritoneal liposarcomatosis; hemorrhagic pulmonary edema; bilateral lobar pneumonia; and generalized hemosiderosis.

Case 15. (PH 864297.) A 63-year-old white man underwent left nephrectomy in 1947 for tuberculosis. In 1948 it was noted that he had a stricture at the right ureterovesical junction; cutaneous ureterostomy was performed and a 16F whistle-tip catheter left indwelling. Secondary pyelonephritis developed in the right kidney, chronic and acute; urine culture never revealed M. tuberculosis but yielded a copious mixed flora of E. coli, B. proteus, B. aerogenes, and Staph. albus. His blood urea nitrogen was normal immediately prior to cutaneous ureterostomy but was up at 44 mg. per 100 cc in 1950. On oral Na acetate and more careful catheter hygiene his blood urea nitrogen was 27 mg./100 cc in May 1951 at which time, nonetheless, there was a persistent hydronephrosis. This case illustrates that a cutaneous ureterostomy with an indwelling ureteral catheter courts pyelonephritis and hydronephrosis. (See also case 4.)

Case 16. (PH 857750.) In 1947 a 25-year-old Negro was admitted for repeated attacks of pain in the right flank and upper abdomen. He had right hydropyonephrosis secondary to congenital stricture at the pyelo-ureteral junction and left pyelonephritis with a dilated tortuous left ureter. He underwent right nephrostomy with lysis of adhesions about the right pyelo-ureteral junction. Postoperatively he had a stormy febrile course and was discharged on the seventy-sixth postoperative day asymptomatic. He continued thus for 3 years and disappeared in 1950. Upon his return in February 1952 his nephrostomy tube was calcified in situ and had to be removed under anesthesia. He was not dehydrated and his blood urea nitrogen was 132 mg./100 cc and blood pressure 110/60. Other laboratory data were thus: $[HCO_3]_s$ 9 mEq/L, $[K]_s$ 7.3 mEq/L, $[Cl]_s$ 103 mEq/L, $[Na]_s$ 120 mEq/L, $[Ca]_s$ 4.4 mg./100 cc, $[\text{inorg. P}]_s$ 15 mg./100 cc, and $[\text{protein}]_s$ 7.1 gm./100 cc. In spite of the marked hypocalcemia he had no signs of increased neuromuscular irritability. Thus, his deep reflexes were even hypo-active and he had no Chvostek or Trousseau sign. It was considered that the acidosis and elevated $[K]_s$ counterbalanced the excitatory effect of hypocalcemia (cf. also Engel and Martin, '48). Treatment was intravenous Na lactate and Ca gluconate and later Ca lactate orally (4 gm. daily in divided dosage) and Na acetate (30 mEq t.i.d.) orally. Basaljel ($Al_2(CO_3)_3$ suspension of Wyeth) 30 cc t.i.d. to reduce alimentary absorption of phosphorus and thus help in lowering the $[\text{inorg. P}]_s$. He was discharged home on the twenty-ninth hospital day, at which time his blood urea nitrogen had stabilized to about 60 mg./100 cc. Other data were as follows: $[Na]_s$ 142 mEq/L; $[K]_s$ 5.4 mEq/L, $[HCO_3]_s$ 12.5 mEq/L, $[Ca]_s$ 8.5 mg./100 cc, $[\text{inorg. P}]_s$ 3.3 mg./100 cc.

D. UREMIA FROM MISCELLANEOUS ACUTE CAUSES

1. Anuria apparently from gantrisin. Case 17. (PH 067133.) A 56-year-old Negress was admitted to the gynecological service November 1, 1951, for vaginal bleeding and a pelvic mass; she felt very weak and had pain in the lower abdomen. Her blood pressure was 110/80 to 140/90 on admission; her hemoglobin 12.2 gm./100 cc; red blood cells 4.46 by 10^6; white blood cells and differential normal; serology negative. Her fluid intake and output were not recorded. On November 3 she underwent dilatation, curettage, and biopsy of the uterine cervix under intrathecal pontocaine plus epinephrine after medication with seconal, demerol, and scopolamine. Postoperatively she received codeine sulfate and aspirin (60 mg. and 600 mg., resp., q. 4h for pain) and 200 mg. Sod. amytal.

On November 12, because of a spike in temperature, burning at the end of urination, and "pain into the back" she was given gantrisin (sulfisoxazole of Hoffmann-La Roche). The quantity she received was:

Date	Amount in gm.
12 Nov	0.5
13 Nov	2.0
14 Nov	2.0
15 Nov	0.5
16 Nov	2.0
17 Nov	0.5
Total	7.5

The nurses' notes reveal the following:

November 3, voiding O.K. Weak.

November 9, soap suds enemats until clear for Ba enema. Very weak after; refused lunch; slept.

November 12, up and about but very weak; lethargic.

November 15, saline enemats until clear (9 in all) for excretory urogram.

November 17, very weak; unable to hold cup of tea in hand alone. Moans and says weak from enema. Voided only 75 cc very concentrated urine. Gantrisin cancelled.

November 18, indwelling catheter. At 10 a.m. only 10 cc urine since midnight. Foul breath; dyspneic; answers when spoken to. Nonprotein nitrogen, 200 mg./100 cc.

Urological work-up was as follows: Cystoscopy on November 18 at which time her bladder capacity was noted to be normal; she had 30 cc of "residual" slightly cloudy urine; a large extravesical mass was indenting the bladder lining. Cystoscopy was repeated November 18 at which time it was realized that the patient was oliguric. There were 100 cc of brownish turbid urine in the bladder; the trigone was elevated on the right; retrograde pyelography showed normal renal pelves; a 6F ureteral catheter was introduced to 26 cm. bilaterally with ease; very little urine flowed; this was alkaline, cloudy yellow with oxalate crystals 2 to 4 per high-power field of spun sediment. On November 18 she was moaning and dyspneic; her chest was clear to percussion and auscultation except for coarse râles posteriorly; cardiac sounds regular; blood pressure 130/80; respirations 26/min. with expiratory moan; pulse 108/min.; semi-comatose, limbs fall limply when released, Chvostek absent; no tremors. She expired at noon on November 19. On that morning her blood chemistry showed blood urea nitrogen of 127 mg./100 cc, $[HCO_3]_s$ 9 mEq/L, $[CL]_s$ 99 mEq/L; $[\text{creatinine}]_s$ 7.8 mg./100 cc.

Autopsy by Dr. Donald King showed adenocarcinoma of the stomach with extension to the gastrocolic ligament, transverse colon and pancreas, and metastases to the lung, ovaries, uterus, diaphragm, peritoneum, and lymph nodes. The parathyroid glands showed no hyperplasia. "The right kidney weighs 160 gm.; the left weighs 140 gm. They are found embedded in their usual position and appear of normal size. The capsules are smooth, shiny and glistening and are not thickened. They strip with ease. The surface of the kidney appears slightly granular, of a tannish grey color, with no crystals or scarring . . . the corticomedullar junction is distinct. However the cortex measures only 4 mm. The arcuate arteries are not prominent. . . . The calyces and pelves are not dilated or congested" (King).

Microscopically, "the kidney cortex shows many glomeruli appearing without morphological lesion. They are fairly cellular, noncongested, with no thickening of the basement membrane. . . . Most of the proximal and distal tubular lumina are patent and contain a small amount of pink, granular, precipitated protein. The epithelium appears intact. There is some scar tissue in the interstitium and a few lymphocytes, but no acute reaction. The arterioles show slight to moderate arteriosclerosis. In the transition zone between cortex and medulla, one finds that many of the tubules contain pink-staining granular casts. . . . They are probably heme pigment, since they fail to stain with ferrocyanide. Some of the tubules which contain casts show degenerative changes in the tubular epithelium. In a few cases the cells are frankly necrotic and the basement membrane is obviously destroyed. A few tubules show degenerative changes even when no casts are present. It is not easy to identify the injured tubules with certainty, but most of them are probably part of Henle's loop or part of the distal convoluted segment. The phagocytosis of heme pigment suggests that some of them may belong to the proximal segment. . . ." (King).

So far as known no other case of renal shutdown has been charged to gantrisin. Furthermore this sulfonamide has been noted in the urine as crystals only seldom and then solely when given in much larger dosage than to this patient.

2. Ureteral obstruction from carcinoma of the uterus or uterine cervix. Case 18. (PH 070298.) A 51-year-old white woman had carcinoma of the uterus for over twelve months; she was anuric for 3 days owing to total obstruction of both ureters. On November 14, after 36 hours of anuria, her blood pressure was 150/70; her blood urea nitrogen 101 mg./100 cc; $[\mathrm{Na}]_s$ 133 mEq/L, and $[\mathrm{K}]_s$ 7.7 mEq/L. On November 16, the third day of complete anuria, she was still rational and complained of pain in the renal regions. She died in hypotension and cardiac standstill close to the end of a unilateral nephrostomy. The limiting factor was most likely a fatally high $[\mathrm{K}]_s$. In such cases it would probably be worthwhile to treat with sodium carboxylate cation exchange resin to lower the $[\mathrm{K}]_s$ before anesthesia and surgery (see under case 20).

Case 19. (PH 006555.) A 46-year-old white woman had undergone radical hysterectomy for carcinoma of the cervix on August 23, 1950. She underwent postoperative radiotherapy. The postoperative left ureterovaginal fistula was corrected on October 11, 1950 by end-to-side uretero-ureterostomy. Postoperative excretory urography showed good function and structure bilaterally. Three months later she was admitted in uremia and congestive myocardial failure from rheumatic heart disease. She was digitalized and put on a no-salt (0.5 gm. NaCl daily) diet, and given one injection of mercuhydrin. She vomited and was, of course, incontinent of urine. Parenterally she received 2,000 cc 5 per cent dextrose in water and 500 cc 5 per cent dextrose in saline in 48 hours. Her $[\mathrm{Na}]_s$ meanwhile fell from 147 mEq/L to 121.7 mEq/L. On February 5, 1951 bilateral nephrostomy was performed. Pyelography through one or the other nephrostomy tube demonstrated bilateral hydronephrosis and hydro-ureter with obstruction at the sacral promontory well below the uretero-ureteral anastomosis. She continued hyponatremic and extremely weak but markedly improved upon the administration of NaCl. She was therefore taken off a NaCl-poor diet. Her weakness was more marked than her anemia (Hb 10 gm.) and intrinsic disease would indicate. The low $[\mathrm{Cl}]_s$ and $[\mathrm{HCO_3}]_s$ together with her relatively high daily urinary output of Cl (6 to 8 gm.; calculated as NaCl, daily) suggested a salt-losing syndrome. The plan was to give: 1) Cl to cover the daily loss; 2) Na acetate to return the $[\mathrm{Na}]_s$ to normal, and 3) calcium to make up for loss and avoid tetany from alkalinization (5 to 10 gm. Ca lactate daily in divided dosage). She received 6 gm. NaCl daily and 30 mEq Na acetate 4 i.d. 4) When the extracellular electrolyte disturbances were brought into line, K-loss was made up for by giving M/3 K acetate orally.

After 2 months of hospitalization the patient was discharged with a blood urea nitrogen of 14 mg./100 cc, $[\mathrm{HCO_3}]_s$ of 19.4 mEq/L $[\mathrm{Cl}]_s$ of 99 mEq/L and an endogenous creatinine-clearance of 39 cc/min. (compared with an initial postnephrostomy of 13 cc/min.). She could concentrate diodrast satisfactorily for excretory pyelography. Several months later she died of carcinomatosis and autopsy disclosed th ureteral obstruction to be caused by carcinoma rather than by the X-radiation.

The data are insufficient to indicate whether she suffered a postnephrostomy NaCl-losing nephropathy. Her NaCl-balance, when measured, was positive even with a low $[Na]_s$ and $[Cl]_s$. The prenephrostomy low $[Na]_s$ contra-indicates such a lesion. The no-salt diet, mercuhydrin, intravenous dextrose and water, and vomiting were probably the guilty quadrumvirate.

3. Uremia from acute fulminating pyelonephritis secondary to removal of radium implants. Case 20. (PH 077968.) A 70-year-old Negress had an infiltrating tumor of the bladder overlying the right ureteral orifice. Preoperative excretory urography showed entirely no dilatation of the renal pelves or ureters. On February 6, 1952 she underwent suprapubic implantation of radium locally. Twelve radium needles were introduced for 4 days and 16 hours, giving a total dose of about 6,000 r. The patient became weak, disoriented, and restless on the fourth postoperative day. The needles were pulled out through the cystostomy on the fifth postoperative day. On the sixth postoperative day she excreted only 60 cc urine whereas she had excreted 3,300 cc the previous day and had excreted ample urine on the preceding postoperative days (fig. 11). The oliguria lasted only 3 days,

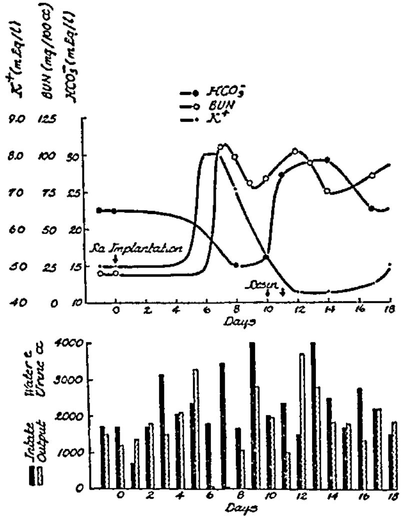

FIG. 11. Case 20. N [illegible] guria upon pulling out radium needles on the sixth [illegible] resin was begun too late to be considered instrumental in causing reversal of abnormally elevated $[K]_s$. Blood urea nitrogen persists elevated in spite of diuresis and correction of acidosis.

present. It is not easy to identify the injured tubules with certainty, but most of them are probably part of Henle's loop or part of the distal convoluted segment. The phagocytosis of heme pigment suggests that some of them may belong to the proximal segment. . . ." (King).

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After 2 months of hospitalization the patient was discharged with a blood urea nitrogen of 14 mg./100 cc, $[HCO_3]_s$ of 19.4 mEq/L $[Cl]_s$ of 99 mEq/L and

The patient's white blood cell count was 24,400/c.mm. with 88 per cent polymorphonuclears. The left renal region was markedly tender but the right was not. On the twenty-sixth postoperative day the ureteral catheters were removed because nothing flowed through them. The patient's total phenolsulfonphthalein excretion was only a trace in 2 hours and he could not tolerate oral fluids. His blood urea nitrogen fluctuated between 45 and 107 mg./100 cc. At the time of death his blood urea nitrogen was close to 107 mg./100 cc and his [creatinine]$_s$ 5.7 mg./100 cc; his [Na]$_s$ and [Cl]$_s$ were within normal limits and he had been excreting nearly 3 liters of urine daily.

The preceding 2 cases indicate that fulminating pyelonephritis can still be fatal to elderly patients even in these days of antibiotics.

5. Uremia from dehydration. Case 22. (PH 602623.) A 71-year-old white woman was dehydrated from lack of fluid intake; hemiplegic and with cerebral arteriosclerosis; mentally unclouded. She excreted only 135 cc urine during the first 30 hours of hospitalization (specific gravity 1.027; acid; white blood cells 4–6 and red blood cells 2–3/hpf; granular casts 3–4/hpf). At admission blood urea nitrogen 41.5 mg./100 cc; [Cl]$_s$ 108 mEq/L; [HCO$_3$]$_s$ 22.6 mEq/L; Hb 15.8 gm./100 cc. The patient was rehydrated slowly with 5 per cent dextrose in water intravenously. Her blood urea nitrogen returned to normal shortly after onset of diuresis:

Hospital Day	Fluid Intake (cc)	Urine (cc)
1	1,620	75
2	2,300	400
3	1,900	1,600+
4	1,930	2,900

Case 23. (PH 091169.) A 78-year-old white woman had long-standing hyperpiesia (blood pressure 170/80); had vomited from urinary tract infection; unable to keep down any food or fluid; reportedly anuric for 5 days prior to admission. Laboratory data on first day were thus: blood urea nitrogen 120 mg./100 cc; [Na]$_s$ 132 mEq/L, [K]$_s$ 6.0 mEq/L, Hb 11.2 gm./100 cc; red blood cells 3.7 × 10^6/c.mm.; no eosinophilia; urine with specific gravity 1.010, acid albumin 2 plus. Cystoscopy on admission showed no obstruction or structural defect but yielded 60 cc cloudy urine. She received 1,500 cc 5 per cent dextrose in water daily. On the first 3 hospital days her urinary output was 45, 350, and 800 cc.

COMMENTARY

1. Renal function in the aged. Tubular function, indicated by maximal tubular excretion of diodrast (diodrast Tm), undergoes greater diminution with aging than does glomerular filtration, indicated by inulin-clearance (Shock, '46). The urea-clearance tends to decline with age after forty (Lewis and Alving, '38). When the obstructed bladder is drained by urethral catheter tubular recovery exceeds increase in glomerular filtration and attains a near-maximum in about a week (Lich, '42). It is empirical clinical knowledge, however, that such recovery may require one or two months (cf. instance, Lapides, '53). The speed of recovery no doubt depends upon satisfactory correction of disturbances in the fluid compartments. Tubular damage with age permits ready loss of Na^+ and Cl^- even at abnormally low plasma levels for these substances. Hence daily urinary outputs of Na^+ and Cl^- may not be used as indications of deficits. Very aged patients who have undergone stress of surgery, as prostatectomy, may develop dangerous hyponatremia (Wilson et al., '51; Bland, '52) with accompanying diuresis, loss of extracellular water, shock, ileus, and rigidity of the abdominal wall. In part this may be due to failure of release of cortisone by the adrenal cortex, i.e. failure of an "alarm reaction," thus producing the opposite of the positive Na-balance which normally follows surgery (Moore and Ball, '52).

Another factor which can cause marked salt-depletion in elderly patients and in patients with chronic renal disease is excessive parenteral therapy with dextrose in water (cf. Fox et al., '52). Impaired response of the aged nephrons to pituitary antidiuretic hormone (White et al., '53) may result in salt and water depletion.

Mercurial diuretics and restriction of sodium chloride in the treatment of congestive myocardial failure are prone to produce loss of extracellular fluid volume with resultant elevation of the blood urea nitrogen and fall in urea clearance (Landis et al., '35; McCance, '36; and others).

The negative balances of electrolyte and water can occur in aged persons due to the following factors: 1) renal tubular failure; 2) adrenocortical deficiency; 3) parenteral therapy with glucose and water; 4) sodium chloride restriction; 5) mercurial diuretics; 6) failure of adequate tubular response to the antidiuretic hormone of the posterior pituitary.

2. Staghorn calculi in patients who are poor operative risks. We have desisted from nephrolithotomy in patients who have large staghorn calculi bilaterally, or unilaterally in a solitary functioning kidney, but who are free from obstruction by calculi (cases 1, 2, 3, 4, 6). In such instances it was believed that nephrotomy for removal of the calculi would produce more renal damage than the renal calculi. Nephrotomy sufficient to almost bivalve a kidney and with the addition of three stab wounds into each half of the divided kidney reduces renal function by roughly 20 per cent at the time of full recovery from the surgical trauma (Maluf, '49). It is contrived to prevent growth of the calculi by specific measures: a) High water intake producing about three liters of urine daily. b) Maintenance calcium diet containing about 600 mg. of Ca daily. This is considered an intermediate level of calcium intake and is just enough to permit Ca equilibrium (Bogdonoff et al., '53). The diet should not yield an acid-ash because it would mobilize calcium from bone and greatly increase the urinary excretion of calcium (Farquharson et al., '31). Similarly, acidifying agents such as NH_4Cl or cranberry juice, and so on, should not be given. c) Reduce alimentary absorption of phosphorus by aluminum compounds: aluminum hydroxide, $Al(OH)_3$ (Fauley et al., '41; Freeman and Freeman, '41; Shorr, '45; Shorr and Carter, '50; Barrett, '48; Marshall and Green, '52) or aluminum carbonate, $Al_2(CO_3)_3$ (Shorr and Carter, '50). The aforementioned workers have demonstrated the efficacy of these aluminum compounds in reducing alimentary absorption of phosphate and markedly diminishing recurrence of phosphatic calculi and their rate of growth. In this respect, $Al_2(CO_3)_3$ (basaljel of Wyeth) is more efficacious than $Al(OH)_3$ (Shorr and Carter). No change occurs in the urinary pH, fasting $[Ca]_s$, $[\text{inorg. P}]_s$, $[HCO_3]_s$, or $[\text{alkaline phosphatase}]_s$. One ounce of the suspension is taken one hour after every meal and once at bedtime. No demineralization of the skeleton has been noted even after seven years of such therapy (Shorr and Carter). The aluminum compounds are also useful in advanced renal failure in diminishing accumulation of phosphate and thus allaying hypocalcemia (Freeman and Freeman). d) Ingestion of sodium acid phosphate (NaH_2PO_4) for diminishing urinary excretion of calcium and acidifying the urine without mobilizing Ca from bone (Farquharson et al., '31; Cordonnier, '48). Some of the $H_2PO_4^-$ combines with Ca in the upper gut and thus reduces the urinary output of Ca while the patient is on a moderate intake of Ca (600 mg.). When the patient is on a low Ca diet (100 mg. daily) most of the ingested $H_2PO_4^-$ is excreted in the urine and there is little further depression of the urinary excretion of Ca (Farquharson et al.). Acidification with NaH_2PO_4 does not mobilize Ca from bone in part because it carries with it available base, Na. Dosage of NaH_2PO_4 is 8 to 15 gm. daily in divided amounts in capsules of gelatine. This medication is probably best discarded if, due to infection, the urine fails to acidify.

3. Sodium acetate and lactate for acidosis. Acetate and lactate are oxidized completely to CO_2 and H_2O relieving Na for excretion with $HPO_4^=$, $SO_4^=$, and organic acids. These compounds not only raise the $[HCO_3^-]_s$ and eliminate fixed acids but, by supplying base, tend to produce diuresis and thus a fall in the blood urea nitrogen. A diseased kidney not only cannot concentrate but it also cannot acidify efficiently, i.e. it fails to manufacture NaH_2PO_4 from Na_2HPO_4. Thus more Na is lost in the excretion of phosphate. If excessive amounts of Na are lost the extracellular fluid diminishes and the renal arterioles constrict (Landis, '35; McCance, '36; Nickel et al., '53). Supplying available Na may thus augment the renal blood flow (Van Slyke, '48). The Na of NaCl is not immediately available for excretion with acid radicals. For the acidosis and renal shutdown which accompany shock, $NaHCO_3$ should be given and not Na lactate, because oxidation of the latter is delayed in shock (Van Slyke, '48). $NaHCO_3$ should be made up freshly; 1.5 per cent is isotonic (Hartmann, '34); it should not be given subcutaneously or intraperitoneally because it is too irritating.

The oxidation of acetate and lactate proceeds through a pyruvate, succinate, malate, oxaloacetate cycle, with release of two molecules of CO_2 during every cycle (Elliott et al., '35; Bloch, '47). Acetate and lactate increase the maximal renal tubular excretion of para-aminohippurate (McDonald et al., '51; Cross and Taggart, '50; Mudge and Taggart, '50) but not the maximal re-absorption of glucose (Mudge and Taggart, '50). There is no specific effect on the renal blood flow or filtration rate. $NaHCO_3$, on the other hand, has practically no effect on renal tubular transfer of para-aminohippurate (McDonald, et al., '51).

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Lactate is ordinarily used and supplied in the racemic form, i.e. r-lactate. Cori and Cori ('29) have found that d-lactate is practically completely utilized in rats (oxidized and deposited as glycogen) whereas a large fraction of the l-lactate is excreted in the urine. Meyerhof and Lohmann ('26) confirmed these findings manometrically using various mammalian tissues. Man, however, is capable of utilizing effectively both l- and d-forms of Na lactate (Hartmann and Senn, '32; Hartmann et al., '38). The amount which is lost in the urine varies with the rate of injection and may not exceed 18 per cent (Hartmann and Senn). The racemic mixture is practically completely metabolized in 1 to 2 hours and the expected increase in $[HCO_3^-]_s$ from r-Na lactate is fairly close to the observed, assuming the CO_2 to disperse into the entire body water (Hartmann and Senn). We have noted this in our own cases, e.g. cases 3 and 4. There is cogent evidence that the HCO_3^- ion, given with Na as lactate, acetate, or simply as HCO_3^-, distributes itself throughout the body water (Gamble et al., '51; Pitts, '53). The Na component, however, probably becomes distributed only in little more than the extracellular fluid or inulin-space (Winkler et al., '43; Deane et al., '51; Pitts '53, and others). The strain on the cardiovascular system resulting from expansion in volume of the extracellular fluid, including the plasma, may thus be almost as great with $NaHCO_3$ as with NaCl (Pfeiffer, '11; Magnus-Levy, '20; Blum et al., '21; Pines and Perera, '49). This point, however, is still in dire need of elucidation. In acidosis, nevertheless, the Na of $NaHCO_3$ would be available for renal excretion and the expansion of the extracellular space would thus be briefer than if NaCl were administered.

The fraction of the bodily weight which is composed of water may be measured by the bodily dilution of a known amount of D_2O, T_2O, or antipyrine and varies inversely with "fatness" (Soberman et al., '49; Osserman et al., '50; Deane, '51; Hardy et al., '51; Prentice et al., '52). It varies from 42 to 71 per cent of bodily weight in males (Hardy et al.) or from 43 to 72.9 per cent (Osserman et al.)., A normal male of average habitus is about 62 per cent water (Osserman et al. '50; Schloerb et al., '50). A female averages about 10 per cent less (Schloerb et al.). A muscular male in good health may be 72 per cent water (London and Rittenberg, '50). Thus a person's habitus should be considered in estimating the total water-content for calculation of deficits in bicarbonate.

Deficiency in Cl is calculated assuming that Cl is dispersed exclusively in the extracellular space. This is at least a rough approximation (cf. Pitts, '53). The extracellular space has been measured by the dispersion of a known amount of intravenously injected inulin, radioactive sulfate, sucrose, bromide, sulfocyanate, or radioactive chloride. The most reliable measurements appear to be with sucrose, radioactive sulfate, radioactive chloride and, perhaps, inulin (Winkler et al., '43; Hardy et al., '51; Deane et al., '51; Walser et al., '52; Threefoot and Burch, '52; Deane et al., '52; Nichols et al., '52; Finkenstaedt, '53). The data are variable and the absolute reliability of the methods is questionable (cf. Pitts, '53). The datum of 20 per cent of bodily weight for extracellular fluid including the plasma (Gamble, '49) has been chosen in our calculations because it appears to be an acceptable mean in "round numbers."

After parenteral correction of acidosis, hyponatremia, and hypocalcemia in patients who had not been able to tolerate oral intake, Na acetate and Ca lactate are administered by mouth. The former is given as a syrup (Fox, personal communication):

Na acetate 1 Mole (= 137 gm.)
K acetate ⅓ Mole (= 30 gm.)
Simple syrup 500 cc
Syrup of lemon water q.s. 1,000 cc.

One cubic centimeter of this solution supplies 1 m/Eq Na^+ and 0.3 m/Eq K^+. The usual dosage is 30 cc 4.i.d., p.c., but the patient may need more and the K acetate may have to be omitted in advanced renal failure if the $[K]_s$ tends to rise abnormally during the trial therapy in the hospital. This syrup may be diluted in ginger ale if it is too objectionable.

Calcium lactate is given orally to maintain a normal $[Ca]_s$, to avert hypocalcemic tetany, and to counteract action of a possibly elevated $[K]_s$ on the heart (cf. Fox et al., '52). Dosage is about 2 gm. t.i.d., p.c. As the lactate, calcium is usually absorbed by the gut (Bauer and Ropes, '26). If the patient is incapable of oral intake and his acidosis has to be corrected parenterally, the calcium is given as gluconate in solution (1 gm. Ca gluconate → 89 mg. Ca). Ca gluconate is usually supplied in 10 cc ampules as a 10 per cent solution. Ten cubic centimeters can be readily injected intramuscularly without pain possibly because of the blocking action of calcium on fine nerve fibers. We have injected 20 cc of 10 per cent Ca gluconate into each buttock without producing pain. The Ca-deficit is calculated as though Ca occupied only the extracellular compartment (e.g. case 3). One or two grams of Ca gluconate are given routinely with every liter of M/6 Na lactate.

4. Administration of glucose parenterally. Glucose has a sparing effect on the catabolism of endogenous protein. A maximal protein-sparing action is obtained by assimilation of 100 gm. of glucose (Gamble, '49). This will minimize release of endogenous $SO_4^{=}$, $HPO_4^{=}$, K^+, and urea and is mandatory minimal intake for every patient. Two liters of 5 per cent dextrose (d-glucose) contain 100 gm. glucose but the solution has to be given slowly enough to allow complete or near-complete assimilation of the glucose. The maximal rate of assimilation of glucose in bed patients is 0.35 to 0.5 gm./kg./hr. (Winslow, '38; Lockhart and Elman, '49) which means that 5 per cent dextrose should be given no faster than 300 to 500 cc/hour. Lockhart and Elman ('49) have shown that amino acids given in combination with glucose solutions tend to increase the rate of utilization of glucose. Insulin will also increase the assimilation of glucose and thus aid in K^+ and $HPO_4^{=}$ uptake by the tissue-cells (Flock et al., '38; Fenn, '40; Bywaters, '44; Finch et al., '46). It is reported that induced hyperglycemia increases the rate of oxygen-consumption by the kidneys and augments the renal blood flow markedly (Levitan, '50).

5. Use of cation-exchange resins in reducing hyperkalemia. Cation-exchange resins are synthetic polymers with sulfonic or carboxylic radicals which interchange H^+, Na^+, K^+, or NH_4^+ ions. From the volumes of the various gastrointestinal secretions given by Gamble ('49), the total daily secretion of K^+ into the gut is about 66 m/Eq, about as much as is ingested on a mixed diet (Black, '53). Re-absorption of this K^+ may be diminished by cation-exchange resins in the H^+, NH_4^+, or Na^+ cycle given orally. Such resins, given in suspension orally or by colonic tube as retention-enemas, are capable of absorbing K^+ in exchange for Na^+, NH_4^+, or H^+ resulting in rise in the fecal loss of K^+ and fall in $[K^+]_s$ (Elkinton et al., '50; Chen and Freeman, '50; Kraus, '50; Dock and Frank, '50; Danowski et al., '50; Gold, '53; especially Evans et al. '53). We have used ammonium carboxylate cation exchange resin No. 648 of Smith, Kline and French Laboratories (see under case 20). Evans et al. ('53) give cogent reasons for using sodium instead of ammonium cation-exchange resin.

The toxic effects of hyperkalemia may be diminished by 1) Ca gluconate intravenously, 2 gm. 500 cc 0.85 per cent NaCl, thus utilizing the antagonistic action of Ca^{++} on K^+ (cf. Fenn, '40; Finch et al., '46); this also makes use of the suppressing action of Na^+ on K^+, especially in cases with hyponatremia (cf. Finch et al.; Amberg and Helmholz, '19; Rosenthal, '43; Hechter et al., '45) and 2) regular insulin, 20 units in 10 per cent glucose in water or isotonic NaCl, thus using supplementary insulin to augment the utilization of glucose and driving some K^+ intracellularly (Bywaters, '44; Keys, '38; Fenn, '40; Flock et al.).

6. Anemia of chronic uremia. Chronic uremia is accompanied by anemia. There is parallelism between the blood urea nitrogen and the degree of anemia not only in chronic glomerulonephritis but in other pathological renal conditions; a hemoglobin about 50 per cent of normal may have the same prognosis as a $[\text{creatinine}]_s$ of 5 mg. or more/100 cc (Brown and Roth, '22; Filo, 37; Parson and Ekola-Strolberg, '33). The anemia is normocytic and normochromic or slightly hypochromic; the plasma-volume typically is normal but the red blood cell mass is reduced, which results in a diminished blood-volume (Emerson, '48).

The anemia is accompanied by depressed erythropoiesis (Brown and Roth, '22; Filo, '37; Loge et al., '50). Typically there are no reparative signs, i.e. there is no reticulocytosis and there is decreased utilization of intravenously administered radioactive iron (Loge et al.). Usually there are no signs of abnormally augmented hemolysis, i.e. the $[\text{bilirubin}]_s$ and fecal urobilinogen are not elevated; the osmotic and mechanical fragility of the patient's red blood cells are within normal limits (Ceconi, '05; Loge et al.); normal red blood cells transfused into these patients survive normally as do the patient's red blood cells in healthy recipients.

Biopsies and autopsies of bone marrow have been equivocal (cf. Sturgis, '48). Piney and Hamilton-Paterson ('46) report that it is not possible to make accurate total cell counts on bone marrow and that such counts vary between 10,000 and 190,000/c.mm. in health depending upon the amount of marrow withdrawn. The differential cell count is more useful but the picture before death is very different from that obtained by the same procedure after death. "In other words, the inferences we may draw from the myelogram are much less certain than those which we may draw from the ordinary blood count." Nevertheless careful studies by Isaacs ('37) and Nordenson ('38) indicate diminished erythropoiesis by showing a smaller number of primitive blast cells and nucleated red blood cells. Leukocytogenesis, however, is apparently not affected (cf. also Brown and Roth) and we are aware that uremia is not typically accompanied by leukopenia. The cause of erythropoietic inhibition is unknown. It is interesting that hypo-acidity of gastric secretion has been found experimentally (Brown and Vineberg, '32) and clinically (Townsend et al., '37) in acidosis.

In cases of nephropathy in which the anemia is rapidly progressive there may be evidence of augmented hemolysis. Normal red blood cells transfused into such patients survive considerably less than 110–130 days but the patient's own red blood cells survive normally in healthy recipients, the hemolytic component being extracellular. Such patients may have reticulocytosis and an elevated $[\text{bilirubin}]_s$. The osmotic and mechanical fragility of the cells is moderately increased (Emerson, '48; Loge et al.). Only in our case 14 was there evidence of augmented hemolysis and this might have been due to the concealed hemorrhage.

The anemia of chronic uremia is refractory to liver and iron therapy. Blood transfusion is of value only in maintaining the [Hb] at 8 to 10 gm./100 cc. Raising the [Hb] to normal does not increase the urea clearance but may do the reverse (Salvesen, '48, and our data with case 14).

7. Double-barrelled ileostomy for intestinal irrigation. Cases 3 and 4, with advanced and progressive failure of a solitary kidney, may have been satisfactory candidates for a 2-meter double-barrelled single-loop ileostomy for intermittent daily irrigations (cf. Twiss, '50; Maluf, '48, '50).

8. The indwelling ureteral catheter in cutaneous ureterostomy. Cases 4 and 15 indicate that an indwelling ureteral catheter is by no means innocuous and that cutaneous ureterostomy with such a catheter is not necessarily preferable to a well performed ureterocolostomy.

SUMMARY

Patients who have undergone prolonged obstruction and/or sustained infection in their urinary tract frequently culminate with irreversible chronic renal failure even after removal of the obstruction or infection.

Such patients may be kept comfortable for years and relatively free from acidosis by the oral intake of Na acetate in palatable form. The Na^+ acts as available base for the urinary excretion of catabolic phosphate, sulfate, and organic acids. The extracellular fluid volume is thus maintained, diuresis promoted, and uremia diminished. If renal failure is not severe, K acetate may be added to combat the tendency for K-loss from alkalosis and Na-intake.

When Na acetate is first administered it will have to be given with calcium salts (Ca lactate orally or Ca gluconate parenterally) to prevent tetany from diminishing acidosis and low $[\text{Ca}]_s$. After the acidosis has been overcome the Ca salts may not have to be given.

Accumulation of phosphate can also be combated by aluminum compounds orally.

Uremia accompanied by nonobstructive staghorn renal calculi should be treated by the following *additional* measures: a) maintenance Ca-diet (600 mg. Ca daily) and b) $Al(OH)_3$ or $Al_2(CO_3)_3$ orally.

Typical treatment of acute exacerbation of uremia and acidosis in a patient

with chronic renal failure aims to a) correct the acidosis and raise the $[Ca]_s$; b) maintain normal $[Na]_s$ and $[Cl]_s$; c) gradually overcome Na-depletion; and d) replenish K-loss from prolonged acidosis. For parenteral replenishment of HCO_3^- the HCO_3^--deficit should be calculated as though HCO_3^- pervaded the entire bodily water and not merely the extracellular fluid. One gram of Ca gluconate should accompany every liter of M/6 Na lactate.

There is no advantage in correcting anemia of uremia by transfusion if the hemoglobin is 8 gm. or more unless major surgery is planned or hemorrhage is imminent.

Fatal hyperkalemia can occur even with daily urinary outputs of 2,000 cc. This is accompanied by advanced renal damage.

Cation-exchange resins of the H^+-cycle given orally or per rectum can lower the $[K^+]_s$ to normal prior to palliative surgery and thus may prevent disaster (case 18).

A patient with advanced renal failure may have a deficit in intracellular K and yet have poor tolerance to K-supplement (30 m/Eq daily) orally (e.g. cases 3, 4, 8 and 9).

A patient with advanced renal damage from long-standing obstruction by a hypertrophied prostate may become more uremic with preoperative urethral catheter drainage but improve with suprapubic cystostomy (case 9).

The $[\text{creatinine}]_s$ and 24-hour creatinine-clearance is a more efficacious method of measuring improvement in renal function than the blood urea nitrogen because the latter may diminish on a low protein high carbohydrate intake, but the $[\text{creatinine}]_s$ or creatinine-clearance remain unchanged (e.g. case 11).

There is either diminished erythropoiesis or no striking change in the cellular differential of bone-marrow in patients with chronic uremia (cases 6, 8, 9 and 13). Even a patient in severe chronic uremia is incapable of responding to allergins by an eosinophilic response of the bone -marrow (case 8). In one instance there was evidence of augmented erythrolysis (case 14) but this may have been due to the concealed hemorrhage.

Acidosis and elevated $[K]_s$ may counterbalance the neuromuscular excitatory effect of hypocalcemia (case 16).

Gantrisin may produce anuria apparently by nephrosis (case 17).

Dehydration from lack of fluid intake can produce reversible severe oliguria or anuria in elderly persons (cases 23 and 24).

Persistent elevation of the blood urea nitrogen in spite of a large urinary output indicates advanced renal damage (cases 2, 7, 8, 9, 11).

Hyperkalemia in spite of a large urinary output, in nontraumatic cases, indicates highly advanced renal damage (cases 6, 8, 9).

The pulling out of implanted radium needles from the base of the bladder may produce severe oliguria followed by fulminating fatal pyelonephritis (case 20).

An indwelling ureteral catheter in a cutaneous ureterostomy disposes to chronic pyelonephritis and nephrolithiasis (cases 4 and 15).

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SIMPLE RENAL CYSTS IN THE NEWBORN
REPORT OF TWO CASES

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Two cases of considerable interest have recently been referred from the Division of Pediatrics, Henry Ford Hospital The first, a solitary simple cyst of the left kidney, is presented because of the paucity of such cases in the literature In 1943 Chalkley and Sutton[1] found only ten cases of solitary renal cysts in children in the literature They added their case of a 13 year old girl with a spontaneously infected solitary cyst The youngest child of their collected series was thirteen months old Braasch and Hendrick[2] reviewed 163 cases of solitary or simple cysts in all age groups in 1944 Of these, two were in children One child was eight months old, the other, 15 months old Smith[3] in 1948 reported the case of a 15 year old boy with an intermittently painful loin mass who came to surgery at the age of eighteen when a solitary simple cyst was found Righini[4] presented a case of solitary renal cyst in a girl of 6 years in 1950, bringing the total reported cases to sixteen Our case makes seventeen

CASE REPORTS

Case 1 K O , No 711838, a newborn female, was found on examination to be a well infant except for a large, firm, movable mass occupying the entire left abdomen Excretory urography (fig 1, *A*) revealed an apparently normally functioning right kidney of normal outline, but nonvisualization of the left kidney A large, round mass could be seen filling the left abdomen, and extending slightly across the midline Cystoscopy revealed a normal bladder The ureteral orifices appeared normal, but an impassable obstruction was encountered at three centimeters on the left A ureteropyelogram (fig 1, *B*) showed marked displacement of the left ureter across the midline to the right and displacement of a hydronephrotic renal pelvis to the right of the midline When the child was 1 month old, exploration revealed the left kidney to be replaced by a single large cyst 12 cm in diameter, containing 150 cc clear, straw-colored fluid No renal parenchyma was found No communication between the cyst and renal pelvis was found The fibrous walled cyst was lined with flattened epithelium A left nephrectomy was performed and the baby made an uneventful recovery

Our second case is one of multiple simple cysts of the kidney This entity is much more common than the previously described solitary cyst

Case 2 R B , No 716572, a newborn male, was found to have a large mass in the left abdomen which was rounded, smooth, firm, and movable Otherwise the

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[1] Chalkley, T S and Sutton, L E Jr J Urol , 50 414, 1943
[2] Braasch W F and Hendrick J A J Urol , 51· 1, 1944
[3] Smith R A Brit J Urol , 20. 8, 1948
[4] Righini, A Clinica Pediatrica 48 663, 1950

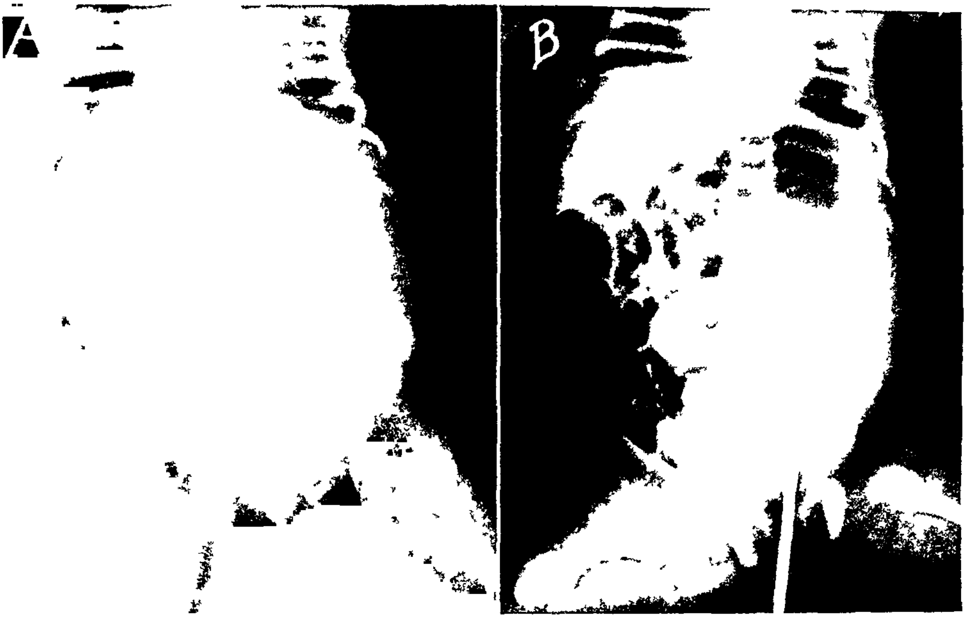

Fig. 1. Case 1 *A*, excretory urogram *B*, left ureteropyelogram

examination was that of a well infant. Excretory urography (fig. 2) showed a normal outline and function of the right kidney, but nonvisualization of dye on the left. The left abdomen was filled with a rounded mass. No left renal shadow was seen. At surgical exploration on the twelfth day of the baby's life, the left kidney was found to be replaced by two large cysts containing seventy and 80 cc clear, straw-colored material, and ten or twelve smaller cysts ranging from 2 mm. to

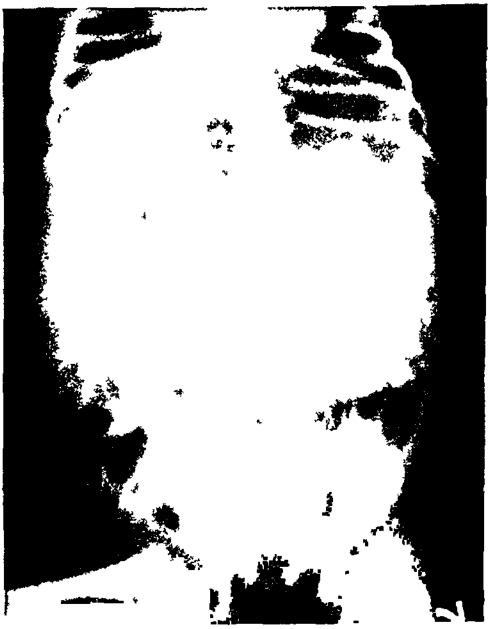

Fig 2 Case 2 Excretory urogram

3 cm. in diameter. A left nephrectomy was performed. A small kernel of compressed renal tissue measuring 3 cm. by 1 cm. by 5 mm. was found near the hilar structures. No communication was found between the cysts and the renal pelvis. The infant made an uneventful recovery.

SUMMARY

The seventeenth case of solitary simple renal cyst in children is reported in a newborn.

A case of multiple simple renal cysts in a newborn is presented.

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BILATERAL POLYADENOMATOUS KIDNEYS; ADENOMATOSIS OF THE KIDNEYS SIMULATING POLYCYSTIC DISEASE

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In the *American Journal of Medical Sciences* for December 1890, an article appeared by Edward Keyes,[1] one of the founders of modern Urology, entitled "Adenoma of the Kidney; Successful Nephrectomy." This is a vivid description of a 49 year old white man suffering from severe gross hematuria and anemia. Under chloroform anesthesia a large right kidney was palpated. This completed Dr. Keyes' investigation, since roentgenography and ureteral catheterization were then unknown. When it is also noted that the field of renal surgery was unexplored and transfusion was impractical, the courage and perspicacity of such pioneering urologists are to be admired. Nephrectomy was sucessfully performed later. The *excised kidney contained an enormous number of adenomas from 2 mm. to 1.5* cm. in diameter. Dr. Keyes' report is the only instance found, in a search of the literature since 1890, which resembles the case to be presented.

CASE REPORT

A 30 year old, single, white man, a crane operator (R-31,300), was admitted to the Veterans Administration Hospital, Fort Howard, Md. on October 14, 1951, with a complaint of painless, gross total hematuria for 24 hours. No other urinary symptoms were present. No history of genito-urinary disease was elicited. It had been noted, however, since childhood, that the left testis was not present in the scrotum. The past history and family history were not pertinent. No evidence of genito-urinary abnormalities in his parents or his three siblings was revealed after careful questioning.

The patient was intelligent and healthy. The temperature was 98.6F, the pulse 84 and the respirations 20. The blood pressure was 158/110. The lungs were clear. The heart was not enlarged but the heart sounds were loud and forceful. There were no murmurs. In each flank there was a large, firm, irregular, nontender mass which was easily ballottable. On the right, the mass extended from the flank to the midline, and from the costal margin well down into the right lower quadrant. It measured approximately 25 cm. vertically and 10 cm. transversely. The mass on the left was similar in all respects except that it was slightly smaller, 20 cm. by 8 cm. These masses were thought to be typical polycystic kidneys. The right testis was normal, but the left testis could not be palpated in the scrotum, inguinal canal or perineum. There was a well healed right inguinal scar. The prostate was normal. The remainder of the examination was normal.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Read at annual meeting, Mid-Atlantic Section of the American Urological Association, Washington, D. C., April 22, 1954.

[1] Keyes, E. L.: Am. J. Med. Sc., **100**: 549–558, 1890.

The roentgenogram of the chest was within normal limits. The serological test for syphilis was negative. The voided urine was grossly bloody and microscopically contained many erythrocytes. The specific gravity of the urine was 1.020, test for albumin was 3 plus, and aerobic and anaerobic cultures were sterile. The hemoglobin was 12.5 gm. per cent; the red blood cell count was 4 million per cmm. and the white blood cell count was 11,650 per cmm., of which 71 per cent were polymorphonuclears, 27 per cent lymphocytes and 1 per cent each were monocytes and eosinophils. The urea nitrogen was 10.3 mg. per cent and the carbon-dioxide combining power 40 volumes per cent.

At cystoscopy, shortly after admission, the lower urinary tract was found to be normal. Efflux from the left ureter, however, was grossly bloody. Indigo carmine appeared in four plus concentration from the right kidney within five minutes; on the left, evaluation could not be made because of admixture of the dye with blood. The retrograde pyelograms (fig. 1) were interpreted as showing typical bilateral polycystic kidneys. A small filling defect in the left upper calyx was thought to be due to blood clot. The excretory urogram confirmed these findings.

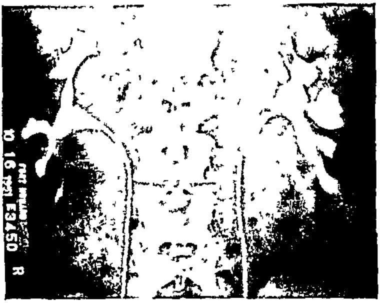

FIG. 1. Retrograde pyelograms

It was felt that the patient had bilateral polycystic kidneys with good function, and that the source of the bleeding was an erosion or rupture of a cyst into the left renal pelvis. Therefore, a conservative policy was carried out. Bed rest, replacement of blood, and vitamin therapy including vitamin K were instituted. During the 45 days after admission, hematuria in varying amounts was almost continuous. Several episodes of cessation of hematuria were accompanied by left renal pain indicative of left ureteral blockage. With the passage of clots, the pain subsided and hematuria recurred. On November 26 an attempt was made to control bleeding by lavage of the left renal pelvis with dilute silver nitrate solution. When this also failed, it was felt that surgical exploration and possible application of Rovsing's procedure were justified. On November 29 exposure was secured through a flank incision. The kidney was four times as large as normal with its surface everywhere studded with firm, rubbery, whitish nodules of varied size. Incision of one of these nodules revealed the same white, rubbery tissue, a portion of which, taken for frozen section, was reported to be "adenoma." Since

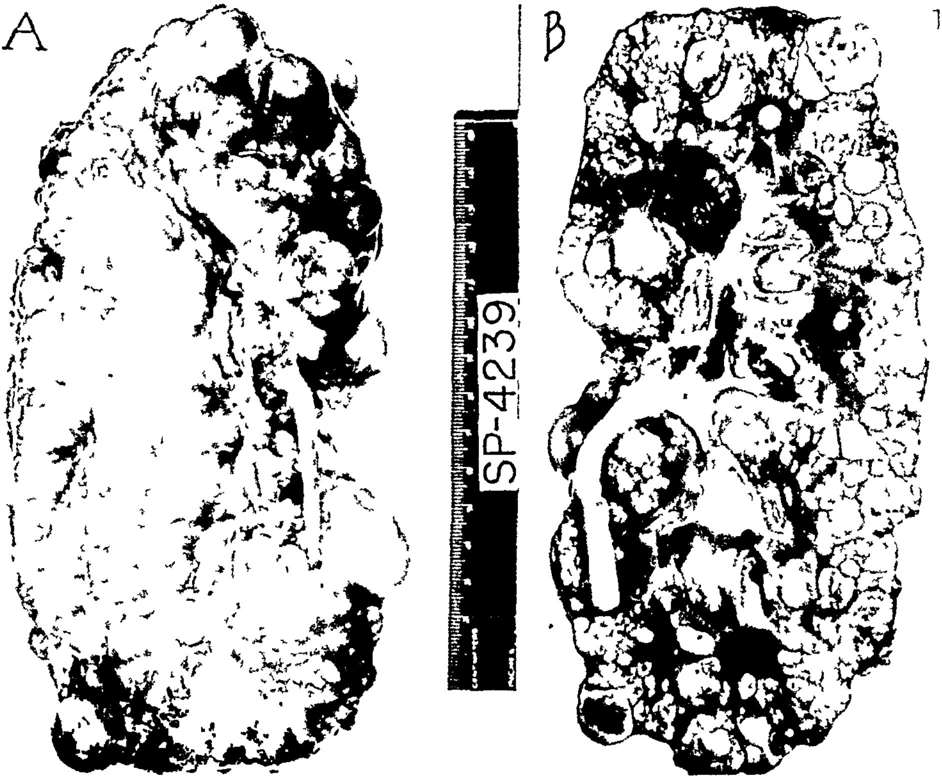

FIG 2. *A*, left kidney, external surface; *B*, cut surface. Note filling defect in upper calyx

the nature and extent of the disease precluded conservative procedure, nephrectomy was performed without difficulty. The postoperative course was without event. Hematuria ceased immediately. The blood urea nitrogen rose to 46 mg. per 100 cc but at the time of discharge had fallen to 33 mg. per 100 cc. Follow-up examinations have been done at frequent intervals. Hematuria has not recurred. The blood urea nitrogen has stabilized at 20–25 mg. per 100 cc. The urine has been negative on routine examination and culture. The phenolsulfonphthalein output is 70 per cent in 2 hours. Urinary concentration however is fixed at a specific gravity of 1.008 to 1.010. The right kidney remains large, hard, and irregular to palpation. Although it undoubtedly duplicates the lesion in its excised fellow, it satisfactorily maintains life. The patient performs a full day of sedentary work and, despite contrary advice, has married.

The kidney (fig. 2) weighed 800 gm. and measured 22 by 9 by 5 cm. Its surface was studded with nodules varying in size from 3 mm. to 2 cm. and, in color, from whitish yellow to dark red and hemorrhagic. On cut section (fig. 2) almost the entire parenchyma was replaced by discrete yellow nodules. The nodules were firm and rubbery, though some showed central necrosis. In the upper calyx there was a dark red protruding mass. Near the hilum of the kidney small areas of normal renal tissue about one cm. across could be recognized.

Microscopically (fig. 3), the nodules were all renal adenomas varying in structure. Some were papillary and some solid. Several showed invasion of their fibrous capsules while others showed calcification or necrosis. The mass protrud-

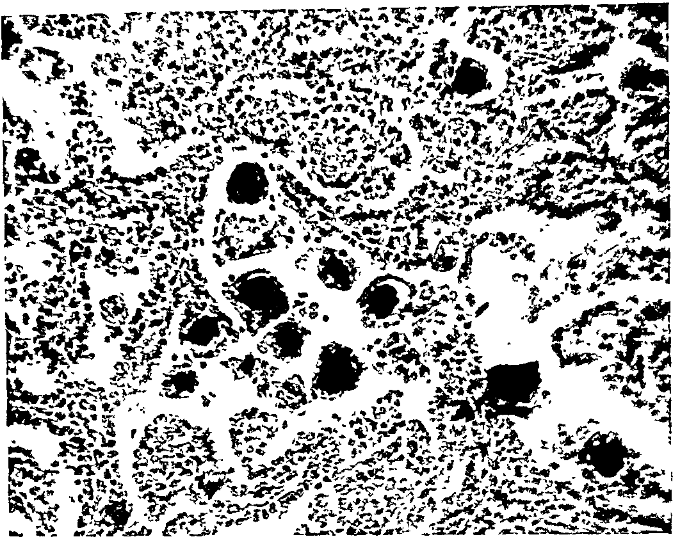

FIG. 3. Typical microscopic section

ing into the upper calyx was a necrotic ruptured adenoma. The pelvic mucosa showed squamous metaplasia and pyelitis cystica.

DISCUSSION

Adenoma of the kidney was first accurately described by Sturm[2] in 1875. The many papers which have since appeared can roughly be divided into two groups. The "clinical" papers report large benign adenoma of the kidney diagnosed during life and requiring surgical treatment. By 1914 Higgins[3] could find only 27 such cases including one of his own. In 1953 the latest reviewers, Childs and Waterfall[4] found 33 reports in the literature and added two of their own. The other, and larger, group of papers deal with "nonclinical adenomas" i.e., those which cannot be diagnosed during life, which are found at autopsy, or in a kidney excised for some other disease. The greatest interest and diversity of opinion appear in the discussion of the histogenesis of this latter group. Most recent students, Ewing,[5] Cristol, McDonald and Emmett,[6] Fuchsman and Angrist,[7] and Gordon,[8] state that these small adenomas occur in kidneys which have been previously scarred because of localized vascular occlusions on an

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[2] Sturm, P.: Arch. f. Heilk., 16: 193–237, 1875.
[3] Higgins, C. C.: Am. J. Surg., 65: 3–14, 1944.
[4] Childs, P. and Waterfall, W. B.: Brit. J. Urol., 25: 187–194, 1953.
[5] Ewing, J.: Neoplastic Diseases. Philadelphia: W. B. Saunders Co , 4th ed., pp. 700–829.
[6] Cristol, D. S., McDonald, J. R. and Emmett, J. L.: J. Urol., 55: 18–27, 1946.
[7] Fuchsman, J. J. and Angrist, A.: J. Urol., 59: 167–173, 1948.
[8] Gordon, B. S.: J. Urol., 59: 1019–1021, 1948.

arteriosclerotic basis. There is postulated first necrosis of tubules due to a small vascular lesion. A tubule becomes fragmented into isolated segments. Apparently the ends of a segment are sealed forming a small cyst, within which the tubular cells then proliferate forming an adenomatous nodule. This theory is fortified by the facts that these tumors are found most often in people over 50 years of age and that they occur in the subcapsular areas where endarteritis would be most evident. They also occur often in association with microscopic cysts presumably also formed by tubular necrosis. Turley and Steel,[9] however, from a careful morphological study of similar material concluded, in their case of multiple miliary adenomas, that the tumors must arise from the glomeruli. Most unfashionable at the moment is the theory of congenital origin. Albarran[10] stated that the precursors of adenomas were islands of imperfectly developed or displaced tubules originating in some aberration of fusion of the nephrogenic and wolffian elements. This latter hypothesis would seem most adequately to fit the present case. The youth of the patient, the diffuse distribution throughout both kidneys, the lack of vascular changes and the lack of correspondence to vascular distribution, tend to confirm the congenital origin of this disease in this patient.

It is felt by many that adenoma may become malignant. Cristol, McDonald and Emmett[6] reported incidental adenomas in 34 per cent of kidneys excised for carcinoma. Others have found adenomas with invasion of the capsule, and have described gradations of cellular architecture from benign to malignant within the same tumor. In the present case no evidence of malignant degeneration was found and after 2 years of observation there is no clinical evidence of malignant disease.

Histologically, adenomas have been classified into three types. The tubular type exhibits long, branching, irregular channels; the alveolar type contains polyhedral cells, arranged more or less uniformly in alveoli; and the papillary adenoma is made up of infolding, branch-like outgrowths often appearing to arise from the epithelium of a surrounding cyst wall. The present case shows all these types in different adenomas and often within the same nodules.

Bilateral involvement of the kidneys by primary neoplasm is frequent in the instances of nonclinical multiple miliary type of adenomas found at autopsy. Less than 30 cases of primary malignant involvement of both kidneys have been reported.[11, 12, 13] Several cases of diffuse bilateral involvement of the kidneys by malignant or granulomatous lesions such as lymphosarcoma, leukemia, round-cell sarcoma and sarcoid have been reported.[12, 13, 14] Unfortunately most of these were autopsy cases and did not have pyelographic study. In a rather careful search of the literature, only one instance was found in which pyelographic findings indicative of polycystic kidneys were found to be due to diffuse involvement

[9] Turley, L. A. and Steel, J.: J.A.M.A., **82:** 857–859, 1924.

[10] Albarran, J.: Quoted by Cristol, McDonald, and Emmett.[6]

[11] Eisendrath, D. E. and Rolnick, H. C.: Textbook of Urology. Philadelphia: J. B. Lipincott Co., 1938.

[12] Forsythe, W. E.: J. Urol., **47:** 784–791, 1942.

[13] Flynn, J. E. and Bowers, J. M.: J. Urol., **58:** 106–111, 1947.

[14] Fischer, G. S.: Grace Hosp. Bull., **26:** 11–24, 1948.

by tumor, in this case, lymphoblastoma (Fischer).[4] It would seem that pyelography, if done more often in diffuse neoplastic disease with renal involvement, might reveal more cases simulating polycystic disease. It is certainly obvious that diffuse neoplastic renal involvement could distort and elongate calyces in similar fashion, and as easily as, cysts. It is also notable that the clinical findings of hypertension, fixed urinary specific gravity, elevated blood urea nitrogen, all consistent with polycystic kidneys, were present in our case.

An accurately descriptive name for this disease was not at hand. It was felt that a parallel could be drawn with the nomenclature of renal cysts. Thus a solitary cyst could be compared with a solitary adenoma and multiple cysts with multiple adenoma. The special appellation for polycystic disease of the kidneys, therefore, logically suggested the parallel term of polyadenomatous kidneys, which was thus adopted as the title of this paper.

CONCLUSION

An instance of bilateral diffuse adenomatosis of the kidneys has been presented. Only one other similar case has been recorded by Keyes in 1890 and, as far as is known, this was unilateral. The distinctive name of bilateral polyadenomatous kidneys has been suggested.

The clinical, urinary and pyelographic changes in this case simulated bilateral polycystic renal disease very closely.

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BILATERAL WILMS'S TUMOR IN A MALE PSEUDOHERMAPHRODITE

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Wilms's tumor associated with pseudohermaphroditism has not previously been reported in the literature. The case to be presented is even more unusual in that the Wilms's tumor was bilateral.

Pseudohermaphroditism is not uncommon, occurring in one out of every one thousand births;[1] but bilateral Wilms's tumor is exceedingly rare. Campbell,[2] in 1948, when reviewing the literature, found 14 cases of bilateral Wilms's tumors. He reported two additional cases of his own. Of the 14 cases appearing in the literature previous to 1948, ten were reported by Walker[3] in a review of the medical literature prior to 1897. Many of these cases were diagnosed by physical examination only and could have easily been polycystic kidneys, hydronephrosis, or some other intra-abdominal tumor. Of the remaining 4 cases reviewed by Campbell, the one reported by Kretschmer and Hibbs[4] in 1931 was probably a metastasis. Riches, Griffiths and Thackray[5] in a review of 189 cases of Wilms's tumor found one that was bilateral and two in which there were metastases to the opposite kidney. Barr and Schulte[6] reported a bilateral Wilms's tumor in 1951.

CASE REPORT

The patient was born October 24, 1950. Its birth weight was 7 pounds, 9 ounces. The child was normal in all respects except for the genitalia. It had a bifid scrotum, undescended testicles and hypospadias with a urethral opening in the perineum at the base of the penis.

The father was 32 years old; the mother was 30 years old and in good health. The pregnancy and delivery were uneventful. The patient had 2 sisters, one 5 years old and the other 8 years old. The mother's first pregnancy ended with the delivery of a stillborn infant at 8 months. There was no family history of any previous congenital abnormalities.

The infant developed normally. It was first admitted to James Whitcomb Riley Hospital on May 12, 1951. A vaginal cystogram made on May 15, 1951 revealed a persistent urogenital sinus into which the urethra and a short vagina

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emptied. In one film there was suggestion of dye in a fallopian tube. The patient was discharged May 19, 1951.

The infant was re-admitted on October 20, 1951. It weighed 20 pounds at this time and was normal in all respects except for the genitalia. A laparotomy was performed on October 22, 1951, for the purpose of ascertaining the true sex of the infant. A small uterus was found, 1 cm. long and ½ cm. in its greatest diameter. Two fallopian tubes arose from the uterus. Near the end of the right fallopian tube was a gonad that looked like a testicle and received its blood

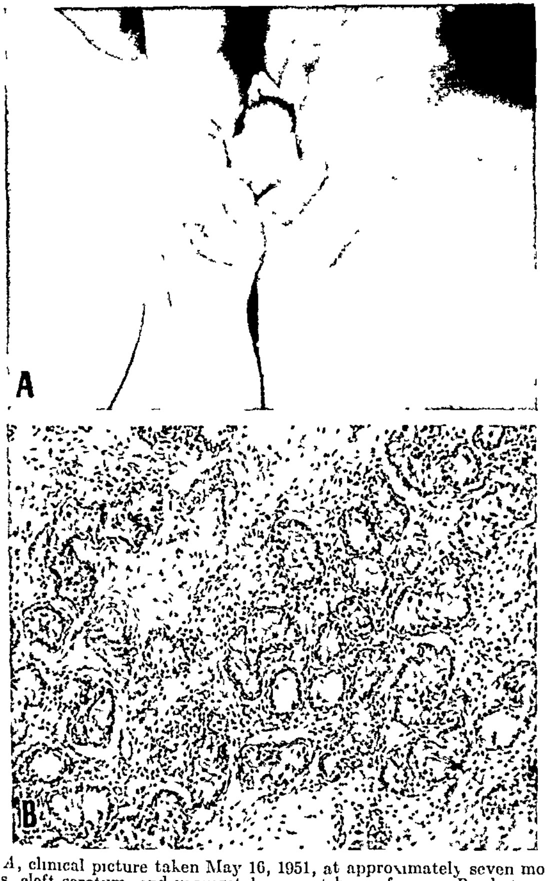

Fig. 1. *A*, clinical picture taken May 16, 1951, at approximately seven months of age. Note penis, cleft scrotum, and urogenital sinus at base of penis. *B*, photomicrograph of biopsy taken from right gonad on October 22, 1951. Infantile seminiferous tubules are easily discernible. Leydig cells are not apparent.

supply from the region of the right kidney. The end of the left tube was adherent to the colon and had to be dissected free. A matted structure that was thought to be a gonad was found at the end of this tube. Biopsies were taken from the gonadal structures. That taken from the right gonad was infantile testicular tissue. Biopsy of the matted structure on the left proved to be primitive oviduct. The infant did well postoperatively and was discharged on October 31, 1951. It was planned to have the patient return at a later date for an attempt to find the left gonad.

The patient was not returned to the out-patient clinic as scheduled and was not seen again until referred to the hospital by the family doctor on September 25, 1952. The child had progressed well until 3 months before this time when the parents noticed that it had a loss of energy and that it was developing a swelling in its abdomen. Physical examination revealed a mass occupying the entire left upper quadrant. Attempted retrograde pyelograms were unsuccessful due to the anomalous urethra and urogenital sinus. An excretory urogram revealed a large, diffuse mass in the left lower quadrant. Only two or three slightly dilated minor calyces were visible on the left. The right kidney showed a moderate dilatation of the lower calyces plus a double renal pelvis.

A total of 1660 gamma roentgen units were given the tumor mass over a nineteen-day period without any reduction in its size. A transabdominal nephrectomy was done on September 17, 1952.

The tumor mass, together with the kidney, measured 17 by 10 by 8 cm. and weighed 900 gm. The entire mass including the kidney was well encapsulated. The capsule was intact. Grossly and microscopically, the tumor had the appearance of a typical Wilms's tumor with nearly all types of tissue described in a Wilms's tumor present, including small tubules surrounded by spindle-shaped primitive connective tissue cells, myxomatous tissue and smooth muscle. On the posterior surface, near the mid-zone of the tumor, there was a small amount of kidney tissue measuring 7 by 5 by 3 cm. and well demarcated from the neoplasm.

The patient withstood the operation well and was started on roentgen therapy again on September 24, 1952. He received 900 units in 11 days. Therapy was discontinued on October 8, 1952 because of the accompanying nausea and vomiting. He improved rapidly following the cessation of the x-ray therapy and was discharged on October 14, 1952, in good condition.

He got along well until November 1, 1952, when he had an acute attack of asthma. The next day, according to the mother, he was unable to void. For the next few days, he passed only a small amount of bloody urine. He was admitted to the hospital again on November 6, 1952. Physical examination revealed a mass in the right upper quadrant and in the right flank. Hirsutism was noted on this admission. The nonprotein nitrogen on admission was 133 mg. per 100 ml., and the serum potassium was 7.7 mEq.

Attempts to do a retrograde pyelogram were again unsuccessful. On November 7, 1952, an exploratory operation was done through a right flank incision. A tumor on the right kidney was found which extended from the liver to the pelvic rim. The ureter was tortuous and distended almost to the size of the large intestine. The ureter was incised and gray necrotic tissue protruded from the incision. Urine began to flow from the ureter as the necrotic tissue was removed. Following surgery, urine drained from the wound. The blood pressure increased to 220/160 mm. of Hg, but dropped to 170/125 in the next 24 hours. The patient's temperature remained normal and he began taking some food. By November 15, 1952, urine continued to pass around the Penrose drain

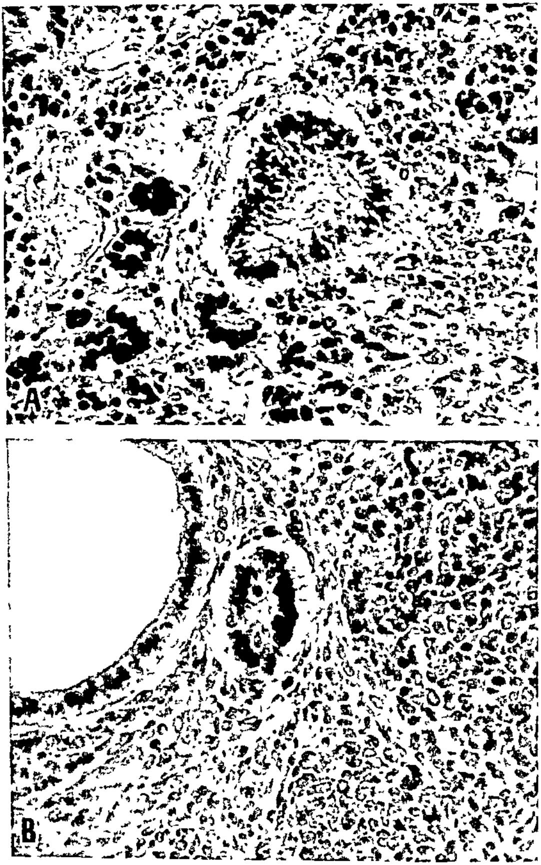

FIG. 2. *A*, photomicrograph of Wilms's tumor on left, removed at surgery. Tubular structures surrounded by spindle shaped connective tissue cells are demonstrated in this area. *B*, area in right Wilms' tumor, removed at autopsy, showing similarity to first tumor shown in *A*. In addition to tubular structures and spindle shaped connective tissue, cystic space lined by columnar epithelium is also present.

and a small fistulous opening in the wound. The blood pressure had decreased to 150/110. A chest x-ray taken on November 7, 1952 demonstrated throughout both lung fields numerous miliary densities which were thought to represent azotemic pneumonia. He was released at the parents' request on November 15, 1952.

The Penrose drain came out and the child ceased to urinate the day he went home. He was re-admitted the next day. His blood pressure on November 16, 1952 was 150/100. Physical examination again revealed the mass in the right flank. Hirsutism was still quite prominent. His urine on this admission was grossly bloody and loaded with pus. The TNPN was 225 mg. per 100 ml. of blood on November 21, 1952. He passed very little urine after he was re-admitted. He took a little food but soon became unresponsive and was sustained on intravenous and subcutaneous fluid. He died on November 29, 1952 at the age of 25 months.

Autopsy findings: A large retroperitoneal mass on the right side extended from the diaphragm to the pelvic rim. This mass consisted of the enlarged right kidney with the central spherical Wilms's tumor. The tumor tissue was 4½ cm. in diameter. The renal calyces showed moderate hydronephrotic changes, although there was no dilatation of the ureter. Scattered throughout the right kidney there were many small abscesses 1 to 3 mm. in diameter.

The left kidney had been removed. There was no evidence of any metastases from either the Wilms's tumor on the right or from the Wilms's tumor which had been removed surgically on the left. The left ureter was found 3 cm. above the left pelvic rim and was normal.

The urinary bladder was normal. There was a small uterus in normal relationship with a vagina. The urethra and vagina met to form a short urogenital sinus. Normal left and right fallopian tubes were present. The testicle was present on the right side in the position that the ovary normally occupies. No gonad was found on the left.

COMMENT

Due to the rarity of bilateral Wilms's tumors and the inability to perform retrograde pyelograms on this patient, the diagnosis was not made when the first kidney was removed. The tumor mass in the left kidney was well encapsulated and gave no evidence of having broken through the capsule at any point. The hydro-ureter and the pelvic changes in the right kidney seen in the intravenous pyelogram were, in retrospect, changes produced by the Wilms's tumor in that kidney.

In this case it is impossible to prove that one of these tumors was not a metastasis from the other; however, Wilms's tumor metastasizing to the kidney is in itself a rarity.[5, 7] The fact that there was no neoplastic tissue anywhere except in the kidneys also implies a bilateral origin. Wilms's tumors usually metastasize first to the lungs, and then to the liver.

Hermaphroditism has interested medical science from ancient times. Many

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races have depicted pseudohermaphrodites in their ancient works of art.[8] The causes of true and pseudohermaphroditism have not been completely solved. It is assumed that sex determination in the human follows the typical mammalian pattern, in which the female sex is determined by the presence of two x chromosomes in the zygote, and the male sex is determined by the presence of a single x chromosome (the y chromosome from the male parent probably being functionless) in the fertilized ovum. It is impossible to determine the sex of the embryo until the sixth week when the embryological seminiferous tubules develop. The ovary does not form structures which positively identify it until the ninth week. The medulla of the gonad differentiates to form the testicle while the cortex first differentiates in forming the primitive ovary. It is believed that the hormone supplied by the medulla, if it is dominant, aids further in establishing male characteristics.[9] True hermaphroditism is probably a genetic factor. Pseudohermaphroditism is probably produced by an excessive stimulation from hormones of the opposite sex from the fetal gonads.[10] Thus, if there are excessive androgens in the case of the female embryo or excessive estrogens in the case of the male embryo, a pseudohermaphrodite will result.

This had been demonstrated by Greene, Burrill, and Ivy[11] in rats and by Hamilton and Wolfe[12] in mice. If androgens are given a pregnant rat early in pregnancy, a retention of the upper wolffian derivatics and an inhibition of part of the müllerian derivatives results. Female offspring of mothers treated with androgens during pregnancy are born with a retention of remnants of the epididymal tract, inhibition of part of the uterine tract, enlarged clitoris, large labia and occasionally with an agenesis of the vagina and sometimes with retention of remnants of the prostate. If estrogens are given a pregnant rat early in pregnancy, the male embryo shows retention of the upper müllerian derivatives and an inhibition of wolffian derivatives. Estrogens given late in pregnancy cause a retention of lower müllerian derivatives in the male offspring, and an inhibition of parts of the wolffian derivatives occurs. These rats at birth have an inhibition of parts of the epididymal tract, the retention of parts of the uterine tract, undescended testicles, small penis with hypospadias, cleft scrotum and occasionally a vagina. Sometimes no prostate develops. Strangely enough, in female rats whose mothers are given an increased amount of estrogen during pregnancy, the wolffian ducts persist and the urogenital sinus is inhibited. This effect is not seen in the mouse.[13]

In the case of the human pseudohermaphrodite, excessive hormones are available from several sources. In the case of the female pseudohermaphrodite, there is often an associated hyperplasia or neoplasm of the adrenal cortex. In these infants, the adrenal cortex tumors of adults will often produce androgens which can be easily demonstrated.

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Vines (as quoted by Sisk and Cornwell[10]) believed that in some female pseudohermaphrodites there is a persistence of the fuchsinophil cells in the adrenal cortex in embryonic life over a longer period than usual. The adrenal cortical cells containing fuchsinophil granules were believed to have been the cells which produced androgens. These fuchsinophil cells are present in the female embryo from the twelfth to the fifteenth week; and in the male, from the ninth to the twentieth week. Others believe that the fuchsinophil granules are of no significance. Sudds[14] has shown that they occur in the adult about equally in the two sexes. They first appear when an adult is about 25 years old and tend to increase during life. In adults, they are related to age and have nothing to do with sex.

There are some who believe that the adrenal cortex of the embryo can produce estrogen in large enough quantities to cause male pseudohermaphroditism. This has never been clearly demonstrated. Only thirteen feminizing tumors of the adrenal cortex have ever been reported; two in children and eleven in adults.[15] The estrogenic hormones could conceivably come from the cortex of the fetal gonad before it has fully differentiated. Another plausible theory is that the estrogens are supplied in excessive amounts by the mother.

It is interesting that pseudohermaphroditism is associated here with the bilateral Wilms's tumor. Testicular tumors not infrequently develop in male pseudohermaphrodites;[16, 17] however, in spite of the fact that both Wilms's tumor and pseudohermaphroditism are related to a disturbance in the tissues developing from the urogenital ridge, the two conditions occurring simultaneously have never been previously reported.

SUMMARY

A case of bilateral Wilms's tumor in a male pseudohermaphrodite is reported.

We wish to express our gratitude to Frank Vellios, M.D., and John J. Mahoney, Ph.D., for helpful comments and criticism.

Photographs were taken by the Department of Medical Illustration of Indiana University School of Medicine.

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SPONTANEOUS RENODUODENAL FISTULAS

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Fistulas that develop between the kidney and the intestinal tract are rare clinical entities. Although renocolic fistulas have been reported 50 times up to September 1953, renoduodenal fistulas have been reported only 8 times. All the recorded cases of renocolic fistulas have had their origin in the kidney, most being secondary to calculi with pyelonephritis, and in none were they thought secondary to bowel disease. Likewise spontaneous renoduodenal fistulas result from an inflammatory process in the kidney which ruptures into the adjacent duodenum. In the colonic fistulas in practically all cases, the fistula has occurred through the cortex from the calyx rather than directly from the renal pelvis. Many of these kidneys show almost complete replacement of renal parenchyma by fatty and fibrous tissue. There is reason to believe that the same process occurs in renoduodenal fistulas.

Eight case reports of renoduodenal fistulas are found in the literature, two of which have been reported by American authors. The etiologic factors in the previously reported cases include hydatid cysts of the kidney, tuberculosis (4 times, once with calculi), pyelonephritis and perinephritis, and most recently epidermoid carcinoma of the kidney involving the duodenum. Were it not for the fact that such lesions are extremely uncommon yet offer very serious problems in treatment, we would not have the temerity to present a single case report. (See table 1.)

The first patient to be successfully treated by nephrectomy was reported in the American literature by Biondi in 1935. Since then King reported a case in a 62 year old man admitted for another illness without renal or gastro-intestinal complaints. Retrograde pyelogram revealed a fistulous communication between the renal pelvis and the second portion of the duodenum. An upper gastro-intestinal series showed barium in the kidney. Right nephrectomy and fistulectomy with ligation of the tract were successfully accomplished and the patient was cured. One year ago, from the Boston City Hospital, Jones, Melendey and Flynn reported a renoduodenal fistula in a 65 year old woman caused by epidermoid carcinoma invading the duodenum, with renal calculus. At operation duodenotomy and gastro-enterostomy were done. It was thought a postoperative duodenal fistula had developed, although this could not be definitely proven, and the patient expired in the immediate postoperative period.

In only two recorded instances have satisfactory results been attained, both by nephrectomy and closure of the tract. The case to be presented represents a previously unreported chain of events with closure of the fistula accomplished without nephrectomy.

Symptoms may vary from predominantly gastro-intestinal to none at all. Symptoms of renal origin with pyelonephritis and cystitis may predominate as

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TABLE 1

Case	Year	Sex	Age	Etiology	Treatment	Outcome
1. Rayer	1839	F	45	?	Conservative	Died
2. Barlow	1843	F	26	Hydatid cysts	Conservative	Died
3. Bang	1874	F	22	Tuberculosis	Conservative	Died
4..Turner	1893	M	18	Tuberculosis	Conservative	Died
5. Pulvertaft	1935	F	28	Tuberculosis with calculi	Conservative	Died
6. Biondi	1935	F	28	Tuberculosis; ? perforated ulcer	Nephrectomy	Satisfactory
7. King	1950	M	62	Pyelonephritis and perinephritis	Nephrectomy	Satisfactory
8. Jones et al.	1953	F	65	Epidermoid CA and calculus	Gastro-enterostomy	Died
9. Present case	1954	F	33	Pyelonephritis and calculous pyonephrosis.	Operative without nephrectomy	Satisfactory

in the case here reported. On the other hand, symptoms may be wholly intestinal such as severe nausea, vomiting, epigastric pain, diarrhea and weight loss. We would differ with a previous report that physical examination uniformly discloses a patient in poor nutritional balance. Although in one of the reported cases, pressure on a right flank mass initiated vomiting of uriniferous material, others have shown little more on physical examination than a variable sized mass in the right flank.

CASE REPORT

M. B. L., a 33 year old grava 2, para 2 was first seen in June 1949 at the age of 29 because of pyuria. Soreness in the right flank associated with chills and fever had been intermittent over a 9-year period. She had been hospitalized in November 1940 with a complaint of pain in the right costovertebral area of 2 years' duration. Excretory urography at that time revealed poor function on the right with mild hydronephrosis, narrowing of the ureteropelvic area, and dilatation of the remainder of the ureter. The left side was normal. A wax-tipped bougie was passed to 27 cm. up the right ureter without scratch or obstruction. Right ureteral specimen was loaded with pus cells, and the bladder urine contained many bacilli. Retrograde studies revealed no opaque urinary tract calculi. The right ureter was reported to show considerable dilatation throughout its whole length except for narrowing at the ureteropelvic junction. The right renal pelvis was only slightly dilated with slight blunting of the calyces.

The patient was treated with sulfanilamide and the pyelonephritis subsided. Ureteral dilatations and restudy were advised but not done.

The patient was not seen by a urologist again until June 1949 when, because of pyuria, she came under our care. In addition to the foregoing history, further questioning elicited the information that a few years earlier she had experienced a sudden tearing pain in her right flank and abdomen followed by a few days of chills and fever.

Physical examination revealed a healthy looking, moderately obese normotensive woman of 29 appearing to be in good health. A globular, movable, slightly tender mass in the right flank could be ballotted between the examining fingers. There was tenderness to percussion over the right costovertebral angle. Catheterized urine revealed grade IV pyuria. Cystoscopy revealed a thick, purulent fluid issuing from the right ureteral orifice while the left ureteral efflux was clear. Indigo carmine returned from the left side in 4 minutes in good concentration, while none was seen on the right after ½ hour.

Initial film of the urinary tract revealed multiple calculi in the region of the right renal pelvis. The right psoas outline was poorly defined. The left retrograde pyelogram was normal; the right revealed marked irregularity of the ureter with dilatation of the distal portion. Ureteral narrowing was noted immediately distal to the large calculus. The renal pelvis was markedly irregular and showed some dilatation. Skiodan was seen to fill the duodenal bulb from the upper pole region of the kidney. A later film showed that the contrast medium had passed from the duodenal bulb to the region of the duodenal-jejunal junction (fig. 1, *A*).

The diagnoses of renoduodenal fistula with right nephrolithiasis, chronic pyelonephritis, and chronic perinephritis were made and hospitalization was advised. Because she was asymptomatic and faced a serious operative procedure, the patient again refused medical advice.

She was not seen again until February 6, 1953, approximately four years later, complaining of pain in the right flank, pain across the upper abdomen and frequency of urination with hematuria of 2 weeks' duration. In the meantime the patient had had another baby 3 years' previously and was now 3 months' pregnant. After consultation with her obstetrician who thought surgery was not contra-indicated, she was admitted to the Wesson Memorial Hospital in February 1952. Excretory urography showed no function on the right side (fig. 1, *C*), normal on the left. The calculi on the right, previously noted, were slightly larger than those seen 4 years previously. Right retrograde study again revealed the renoduodenal fistula (fig. 1, *B*). Gastro-intestinal series showed a tenting of the second portion of the duodenum posteriorly on a lateral film, but no barium entered the urinary channels (fig. 1, *D*). A large gallbladder filled with calculi was noted. Urine culture revealed E. coli. Red blood cell count was 3.5 million with 61 per cent hemoglobin or 9.6 grams.

Right nephrectomy was planned after correction of the anemia by blood transfusions. Through a right lumbar incision with subperiosteal resection of the eleventh rib, the right flank was explored. No recognizable kidney tissue could be found. Instead a grapefruit-sized, densely hard fibrolipomatous mass was found. Into this mass medially a loop of duodenum entered above and emerged below. The bowel was so densely adherent that no separation from the mass was possible, short of sharp excision. Due to the fixation of the tissues, it was felt that it was technically impossible to remove the mass in which had been the original kidney. The ureter was followed up to the mass, the large calculus palpated in the area of the pelvis, and the fibrolipomatous covering incised about 2.5 cm. in depth before the stone could be freed. After the large calculus and several small

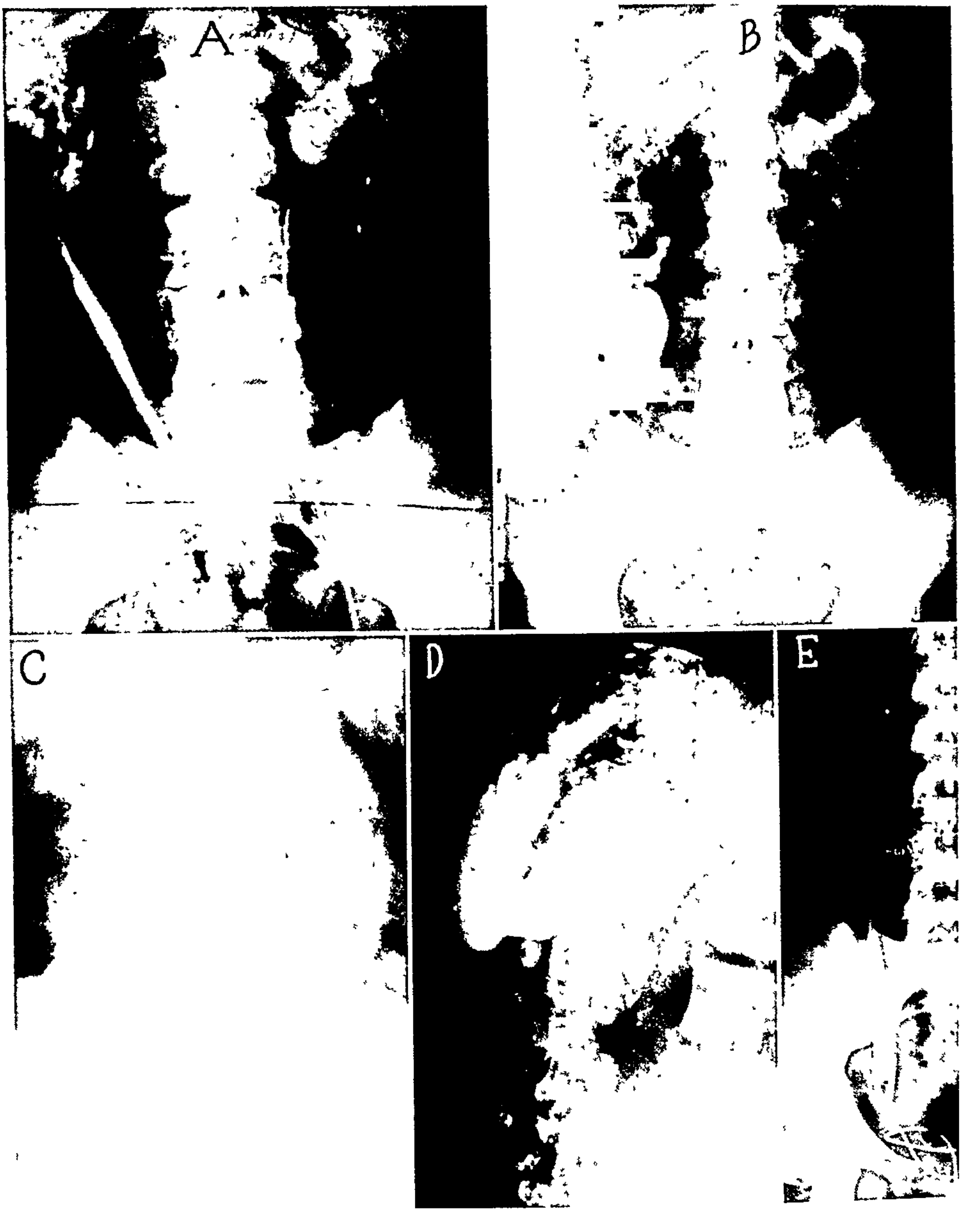

FIG. 1. *A*, preoperative re[illegible] 1949, in which injection of skiodan was done on right side only a [illegible] injection. Dye filled small bowel in region anterior to left kidney. *B*, preoperative retrograde pyelogram, right, February 1953, showing filling of first portion of duodenum. *C*, excretory urogram, February 1953, showing normal left pyelogram, and renal calculi with no diodrast excretion on right. *D*, upper gastro-intestinal series, lateral view, showing tenting posteriorly of second portion of duodenum due to renoduodenal fistula. *E*, postoperative retrograde pyelogram, right, showing residual renal pelvis, with absence of communication between kidney and small bowel.

calculi were removed, probing failed to reveal any tract leading either upward or medially. At this point it was decided 1) to abandon further attempts at separation of the mass from the bowel, and 2) to allow the pyelotomy to remain open and hope for autonephrectomy with closure of the fistula spontaneously.

A Penrose drain was placed to the pyelotomy site and the wound closed. The postoperative course was uneventful and the patient was discharged on the fourteenth postoperative day.

Crystallographic analysis of the calculi by Dr. Edwin Prien was reported to show stones of different composition. One contained calcium phosphate with trace of calcium oxalate and another was composed of a colloidal type of apatite or calcium phosphate found usually in bone or in the nails or other horny structures. Dr. Prien guessed that the patient ate some such substance which passed from the duodenum into the kidney.

The patient continued to have a small amount of greenish, purulent drainage from the flank, not duodenal at any time, requiring a change of dressings every day to every other day. Three months postoperatively homologous serum jaundice developed and subsided under medical treatment. Six months postoperatively, one month after an uneventful delivery, cystoscopy was done in order to demonstrate the right ureter and pelvis. For technical reasons the catheter would not pass above 2 cm. It was then decided to close her external sinus tract with streptokinase and streptodornase. After 48 hours of 3-hourly irrigations with this enzymatic mixture, by the patient, the tract closed and remained closed. Cystoscopy and right retrograde pyelograms were repeated 8 months postoperatively and showed closure of the fistulous tract, with nonfunctioning pelvis and pyo-ureter (fig. 1, *E*). These studies were repeated 1 year postoperatively and again showed closure of the fistulous communication.

The patient now complains of occasional backaches which are relieved by passage of a 8F ureteral catheter with lavage of the right pelvis and ureter at 4–6 week intervals. There are no bladder symptoms and as would be expected, the infection is resistant to therapy. In all likelihood, she will require excision of the pelvis and ureter on the right before a complete cure can be accomplished.

DISCUSSION

Renoduodenal fistulas have been shown to occur secondary to an inflammatory process in the kidney with rupture of a parenchymal abscess through a calyx into the duodenum. Anatomically the anterior surface of the kidney in the region of the hilum is in direct contact with the second portion or pars descendens of the duodenum. The bile duct and the pancreatic duct open into the descending portion of the duodenum a little below its middle. The intimate relations of the duodenum to the right kidney are attested to by the well documented reports of duodenal injury secondary to right nephrectomy. Duodenal fistula is a serious complication of duodenal surgery and right renal surgery, and should be meticulously avoided.

SUMMARY

A ninth case of spontaneous renoduodenal fistula with discussion of the entity is presented. The pathogenesis of the lesion can be traced from pyelonephritis through perinephritis with probable rupture through a calyx into the duodenum. Although fixation of tissues made safe removal of the remaining renal mass impossible, conservative operation followed by obliteration of the lumbar sinus tract succeeded in closing the renoduodenal fistula. These lesions have been cured by nephrectomy in only two reported cases, while this case represents the first reported cure of the fistula by conservative surgery. Wherever possible, the treatment of choice is nephrectomy with closure of the fistulous tract.

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A SPIRAL FLAP PYELO-URETEROPLASTY FOR LONG NARROWINGS OF THE UPPER URETER

MILTON E. GORDON

The purpose of this report is to describe a simple new variation of the flap type pyelo-ureteroplasty that is applicable to long narrowings of the upper ureter. Until now this condition has had no adequate surgical repair except for the Davis intubated ureterotomy which requires a long period of intubation and nephrostomy drainage and is prone to cause stone formation and infection. The spiral flap pyelo-ureteroplasty was devised to make the prolonged use of these tubes unnecessary thereby reducing the frequency of these complications and lowering morbidity even if these complications do not ensue.

The spiral flap requires a certain minimal amount of redundant renal pelvis, a condition that is usually present due to back pressure and consequent pyelectasis. With other pyelo-ureteroplasties, much of the redundant renal pelvis is wasted and cannot adequately be mobilized when the narrowing of the ureter involves too long a segment. The spiral flap procedure permits mobilization of all available renal pelvis.

PROCEDURE

The renal pelvis is amputated obliquely about 0.5 to 1 cm. above the ureteropelvic junction. The flap is formed from the renal pelvis simply by cutting in a spiral manner starting at the distal amputated end and continuing the incision around the renal pelvis parallel to the amputated border fashioning a strip about 1 cm. wide (fig. 1). The narrowed area of the ureter is then incised for the length of the narrowing plus an additional centimeter. The long flap from the renal pelvis is sutured to the incised portion of the ureter over a ureteral splint (fig. 2). The redundant opening of the renal pelvis is closed after insertion of a nephrostomy tube.

Although serious doubt may be felt about the viability of such a long flap obtained in this manner, the case report presented below would help to dispel that doubt. However, if in the course of forming such a flap it becomes apparent that the blood supply to the flap has been compromised, a re-anastomosis of the distal amputated renal pelvis can easily and quickly be done, and the Davis intubated ureterotomy is still applicable.

CASE REPORT

M. G., an 18 year old man, reported to the clinic with a one month history of repeated passage of clots in the urine and of three episodes of total gross painless hematuria, but no other urologic symptoms. Urinalyses showed persistent low grade microscopic hematuria and a urine culture grew nonhemolytic Staphylococcus aureus, probably a contaminant. The urogram showed a normal collecting system on the right while the left side showed marked caliectasis. Since

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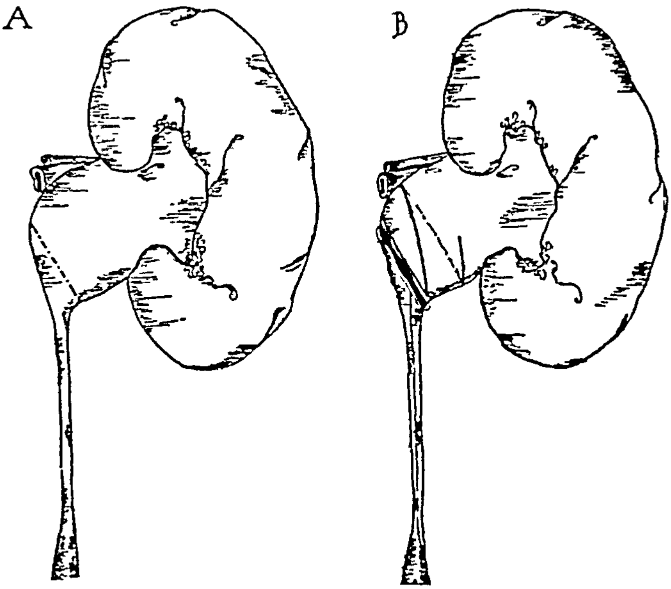

FIG. 1

the films were discontinued after 15 minutes, the renal pelvis was not visualized or the left. A left bulb retrograde pyelo-ureterogram showed marked left hydronephrosis with marked narrowing of the left upper ureter for 8 cm. (fig. 3, *A*). After the retrograde study, the patient experienced left costovertebral angle pain and tenderness for the first time in his life. He was placed on aureomycin to prevent infection. An operation was performed on February 18, 1954.

The kidney, renal pelvis and upper ureter were exposed through the usual kidney incision, removing a portion of the twelfth rib. The upper ureter for a distance of 7 cm. was thin and vas-like to palpation, and was visibly much more narrow than the more distal ureter. The renal pelvis was not so abundant as was

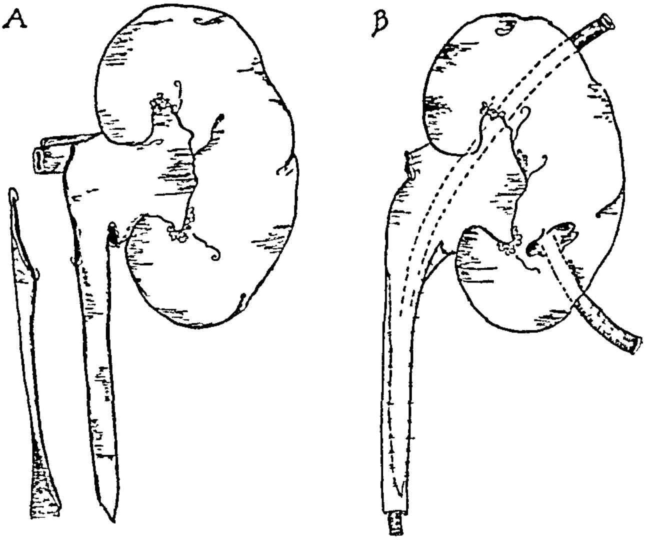

FIG. 2

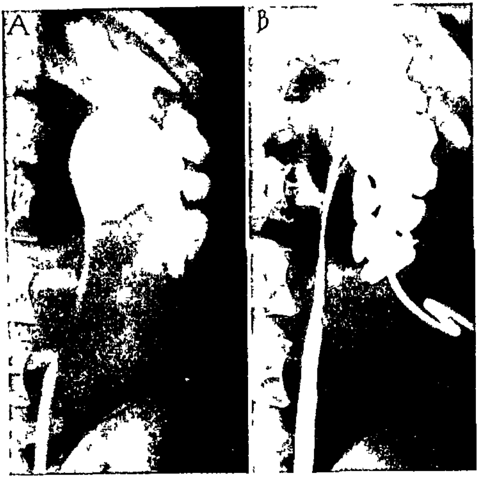

FIG. 3

expected from the preoperative pyelogram, but extended about 4 cm. from the hilus when traction was placed on it and measured about 3 cm. across in its widest, most proximal portion. The pelvis was then amputated as previously described and a 10F Robinson catheter was passed down the ureter with moderate resistance. There was no other evidence of obstruction. Combined internal and external palpation of the kidney revealed many areas of greatly thinned out parenchyma, but there were many areas that seemed to have good functioning tissue. A nephrostomy was performed and a spiral flap 1 cm. wide was cut circumferentially as previously described. Eight centimeters were easily obtained and it was estimated that another 8 to 12 cm. readily could have been mobilized if needed. The upper ureter was incised including 1 cm. of normal ureter, and as flattened out was only 5 mm. in diameter. The pelvic flap was then sutured to the incised ureter over a 330 polyethylene tube and the redundant pelvic opening was closed. At no time did the blood supply to the flap seem impaired and at the end of the plastic procedure the color of the flap was as good as that of the ureter and pelvis.

Postoperatively, despite large doses of chloromycetin and gantrisin used prophylactically, basaljel, hyaluronidase and a large fluid intake, the urine from the nephrostomy tube became markedly cloudy and loaded with pus. The ureteral splint was removed on the fourteenth postoperative day after a routine x-ray film showed no evidence of stone formation. A descending pyelogram through the nephrostomy tube, made a few minutes after removal of the splint, showed prompt passage of the contrast medium down the ureter and into the bladder (fig. 3, *B*). Considerable caliectasis remained, but the caliber of the upper ureter appeared to be improved over that seen preoperatively. The nephrostomy tube was removed and within a few hours the wound became and remained dry, but the patient began to complain of severe dysuria. The dysuria ceased after two days, but the urine sediment showed marked pyuria. The antibiotics were discontinued long enough to get a urine culture which grew paracolon bacillus, resistant to all antibiotics tested except for moderate sensitivity to furadantin. Furadantin was administered whereupon the pyuria was reduced from fields loaded with pus cells to 8–12 per field.

COMMENT, SUMMARY AND CONCLUSION

If the presence of a ureteral splint and nephrostomy tube in a greatly dilated kidney can lead to severe infection in 2 weeks, it seems apparent that the presence of these foreign bodies for periods of two to six times as long, as recommended for the intubated ureterotomy, would increase the danger of infection by at least two to six fold for that type of operation. The possibility of stone formation with or without urea splitters is also increased thereby seriously jeopardizing the success of the Davis operation. The earlier removal of these foreign bodies made possible by the spiral flap pyelo-ureteroplasty would make this procedure the one of choice for long narrowings of the upper ureter.

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TREATMENT OF ENURESIS IN FEMALE CHILDREN

A C ABERNETHY AND E M TOMLIN

From the Department of Urology, United States Naval Hospital, Bethesda, Md

Enuresis has been recognized as an important symptom complex since the earliest published literature The Papyrus Ebers, written about 1550 B C , prescribed a remedy for "incontinence of urine "[1] It has been defined as the involuntary discharge of urine after the age of three years That age has been rather well accepted as the time when normal children acquire the ability to control micturition The incidence of enuresis has been variously reported as sixteen to twenty-six per cent of children, however, it is estimated that there would be a much higher incidence if all children with enuresis were seen by a physician Nocturnal enuresis alone occurs in approximately sixty to eighty per cent, and diurnal enuresis alone in only five per cent Twenty to forty per cent may have both [2]

The etiology and pathogenesis of enuresis are not definitely established as demonstrated by the varied theories offered by the numerous contributors on the subject in the literature Obviously, the cause is not the same in each child Enuresis is only a symptom, and it is the responsibility of the pediatrician, urologist and psychiatrist to discover the immediate cause in each case

Bakwin[3] has listed four principal theories of pathogenesis as follows: The urologic viewpoint which holds with the early students on this subject that enuresis is due to an anatomic defect, the theory of Holt and Howland that enuresis is an undesirable habit, the result of improper training, the psychiatric school that enuresis is a disorder of personality, and his own theory that enuresis is an hereditary abnormality in bladder function, the foremost characteristic of which is an urgent need to empty the bladder

The importance of correction of the enuretic problem is obvious It is essential for the normal mental development of the child and his acceptance in any society that he be continent of urine It is important for the peace of mind of the parents that their child be normal in this respect It is even more important that this symptom, rather common in children, not be carried into adult life where the individual with enuresis is even more a social outcast than he was as a child, and in whom failure to correct an organic lesion in the urinary tract may well lead to permanent damage

The treatment of enuresis has been as varied as the theories concerning its pathogenesis have been numerous Treatment has progressed from the use of juniper berries, cyprus, and beer in the sixteenth century B C ,[1] the use of a

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The views expressed are those of the authors and are not to be construed to represent those of the United States Navy or of the Naval Service at large

Read at annual meeting Mid Atlantic Section of American Urological Association, Washington, D C , April 22, 1954

[1] Glicklich L G An historical account of enuresis Pediatrics, 8 859 876, 1951

[2] Campbell M Clinical Pediatric Urology Philadelphia W B Saunders Co , 1951

[3] Bakwin, H Enuresis in children J Pediat , 34 249–262, 1949

burned, powdered cock's trachea in the sixteenth century A.D.,[1] to the numerous methods employed today. In addition to treating any generalized illness in the child, modern treatment may consist of psychotherapy, rewards, conditioned responses, medical management, or local urological treatment of organic lesions. The psychotherapeutic approach is based on the belief that enuresis is the symptom of a basic personality disorder. The use of various electrical apparatuses is an attempt to condition the child to awaken from the ringing of a bell or lighting of a light when he begins to micturate in bed, and thus overcome his enuresis. Medical management has included attempts to prevent the child from sleeping so soundly, attempts to increase the irritability and thus the sensation of a full bladder, hormonal therapy, and antispasmotic drugs including belladonna and, more recently, banthine.[4] Each of these methods has been reportedly successful on some cases.

But since it is a well recognized fact that enuresis is only a symptom of some underlying disease, then it is obvious that, as in all other symptom complexes, the underlying etiology should be first determined in an attempt to decide whether or not the projected therapy will be treating the underlying cause. If the enuresis is, as many feel, simply an undesirable habit trait from poor training, then the mechanical methods of awakening the child with nocturnal enuresis should be sufficient. If the enuresis is due to a personality disorder, then psychotherapy is indicated. However, if the enuresis is on the basis of an organic pathologic entity, whether that be inherited, congenital, or acquired, that entity must be found and treated, not only to relieve the child of his immediate problem, but to prevent permanent or longstanding damage to the urinary tract.

We do not feel that all enuretic children, or all enuretic female children necessarily have organic disease. However, we do feel that a rather high incidence of urethral and bladder disease will be found if these children, whose primary admission symptom is enuresis, are completely studied. In the past, there has been a reluctance on the part of the parent and the doctor to submit an enuretic child to a complete urological workup which would involve pain and an anesthetic. With modern cystoscopic instruments, advances in anesthesia, and improved urographic media, the problems of a complete urological examination have been minimized.

Campbell,[2] Bakwin[3] and Everett[5] all state that enuretics who do not respond to routine pediatric treatment within two to three months, or who have pyuria along with their enuresis, should have cystoscopic examinations. This contention we have followed, and have received excellent co-operation from the pediatric clinics in Naval Medical facilities in our area.

In the Urology Clinic at the U. S. Naval Hospital, Bethesda, Maryland we have followed a routine practice of obtaining excretory urograms and performing panendoscopy on all enuretic children referred to us. General anesthetics have been required for panendoscopic examination on the younger children Some of the older children have been very co-operative with only topical anesthetics We do not feel that we have inflicted any serious psychic trauma on any of these children

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[4] O'Malley, J. F. and Owens, R. H.: Banthine therapy for enuresis. Mo. Med., 50: 188–189, 1953.

[5] Everett, H. S.: Gynecological and Obstetrical Urology. Baltimore: Williams and Wilkins Co., 1947, p. 239.

The incidence of organic disease we have found is much higher than that reported by most contributors, possibly because only refractory enuretics or those with pyuria have been referred to us by a number of pediatric clinics, and we have no way of ascertaining the total number of enuretics seen by those clinics, nor the percentage of their refractory cases that we have seen

We are limiting our discussion to the female enuretic children treated in our clinic during the past 2 years, because each case appeared to follow a very similar pattern The commonest lesion found was a narrow urethra, with resultant edema of the bladder neck, low-grade chronic trigonitis, and, in many, the bladder wall had become trabeculated to overcome the narrow urethral outlet These findings are not peculiar to enuresis A number of articles recently have been published drawing attention to similar findings in female children as the cause for chronic recurring infections We feel that there is a definite relationship between the problem of the refractory enuretic child and the child with recurrent urinary tract infections The treatment is very similar, i e , the eradication of infection and the dilatation of the urethra as many times as is indicated along with bladder dilations when indicated The use of banthine or other antispasmotic drugs along with local treatment of the urethra and bladder will undoubtedly result in the highest percentage of cures of these combined problems

During the past 2 years, nineteen female children, ranging in ages from 3½ to 10 years, have been referred to us with the primary problem of enuresis Of this group, seventeen had only nocturnal enuresis, and two had both nocturnal and diurnal enuresis Eighteen had been enuretic since birth, and one had become enuretic six months prior to our examination, following an episode of measles Seven had no complaints other than enuresis, nine had recurrent cystitis, two had recurrent cystitis and pyelonephritis, and one was seen in acute urinary retention

Excretory urograms and panendoscopic examinations were performed on each of these children as soon after the first visit as was compatible with the state of any infection persent

The results of the excretory urograms showed evidence of chronic pyelonephritic damage to one kidney in two of the children Bilateral renal damage was demonstrated in none

Panendoscopic examination revealed the pathological process in one child to be a spastic bladder neck secondary to a spina bifida with damage to the parasympathetic innervation of the bladder In one child, obstruction was found to be due to scar tissue resulting from the removal of a urethral diverticulum 1 year prior to her first visit to us

In fifteen of the remaining cases, urethral strictures required dilation with sounds before a cystoscope could be introduced Edema and evidence of chronic inflammatory changes were felt to be important in 11 cases In 9 cases, trabeculaburned, powdered cock's trachea in the sixteenth century A.D.,[1] to the numerous methods employed today. In addition to treating any generalized illness in the child, modern treatment may consist of psychotherapy, rewards, conditioned responses, medical management, or local urological treatment of organic lesions. The psychotherapeutic approach is based on the belief that enuresis is the symptom of a basic personality disorder. The use of various electrical apparatuses is an attempt to condition the child to awaken from the ringing of a bell or lighting of a light when he begins to micturate in bed, and thus overcome his enuresis. Medical management has included attempts to prevent the child from sleeping so soundly, attempts to increase the irritability and thus the sensation of a full bladder, hormonal therapy, and antispasmotic drugs including belladonna and, more recently, banthine.[4] Each of these methods has been reportedly successful on some cases.

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NEUROFIBROMATOSIS OF THE BLADDER

JOHAN N. DE KLERK AND WILLIAM A. CAMPBELL

From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital, Baltimore, Md.

Bladder tumors, in the great majority, are epithelial in origin, those benign and malignant neoplasms arising from other cellular components comprising considerably less than 10 per cent of the total. Leiomyomas and fibromas are the more common, with angiomas, sarcomas, and the tumors of neural origin being quite rare.[1] A review of the literature to date reveals 14 cases of urinary bladder involvement with neurofibromas, 9 of this series occurring in conjunction with neurofibromatosis of von Recklinghausen. It is probable that only in the latter group of cases, i.e., those with cutaneous involvement, could the diagnosis of the bladder condition be suspected prior to biopsy, and thus a general review of von Recklinghausen's disease and presentation of two cases with bladder neurofibromata is offered.

Von Recklinghausen's paper of 1882[2], with the recognition of the syndrome and its association with the peripheral nerves, was antedated by several reports over the preceding 30 years. Generalized neurofibromatosis is familiar in the picture of multiple subcutaneous tumors and the pigmented *cafe au lait* spots. The tumors, fibroma molluscum, may be pin-head sized or large and pendulous, usually very soft or elastic, and exhibit frequent pigmentary, vascular, or xanthomatous changes. Histologically these may be pure fibromas or show numerous cellular and stromal variations. Deeper, firm tumors more characteristically neural in origin, may be palpable along the course of peripheral nerves. Tumors and pigmentary changes appear usually between the tenth and thirtieth years, affecting any portion of the body surface. The disease is known to have a strong hereditary propensity, seeming to be transmitted by either sex as a Mendelian dominant, some cases being recognized only by the skin pigmentary changes without tumor formation (*forme fruste*). Cirsoid neurofibromatosis and elephantiasis nervorum are other peripheral nerve tumor manifestations wherein the great majority of the nerves of an area are enlarged. In addition to cutaneous forms, systemic changes are usually prominent. Mental deficiencies and aberrations, notably idiocy, are common. Nevi of several varieties are encountered in the skin, and vascular nevi and angiomas affect the circulatory system. Within the central nervous system gliomas and gliosis of different kinds may occur. The bones show hypertrophy, lengthening or dwarfing, cysts, and commonly scoliosis. There may be an endocrine involvement for puberty and pregnancy produce changes, with instances of acromegaly and Addison's disease being noted. Neurofibromatosis of the nerves within the body has been repeatedly reported. In order of frequency, they occur within the cranial cavity and spinal column, in the thorax, in the sympathetic system retroperitoneally, and finally in the intestines and pelvis.

Accepted

[1] Herbut, 1952

[2] von Rec

tions were found in the bladder wall. A reduced bladder capacity was found in four of the cases with capacities of less than 100 cc.

In all of the 19 cases referred to us, some pathologic entity was present which we felt could account for the enuresis. We feel that this may well indicate the possibility that the incidence of local organic disease as an etiologic factor may be much higher than has previously been reported.

Treatment consisted of first eradication, if possible, of any infection present, using appropriate antibiotics or chemotherapeutic agents. Then followed a series of urethral dilations at intervals of 1 to 3 weeks, depending largely on the child's response to therapy. These urethral dilations were carried out in all except one case without anesthesia. The one exception was the youngest child in the group, only 3½ years old. The children were extremely co-operative, most of them eager to report on their progress, and only moderately reluctant to have the painful dilation performed.

Bladder dilations to capacity were performed on the 4 children with small capacities under general anesthetics, on three occasions each.

Of the 19 children treated, fifteen were completely relieved of their enuresis following urethral dilations ranging in number from two to eighteen. Three children had marked improvement in their enuresis, converting from nightly to weekly or bimonthly enuresis, and one was cured of her diurnal enuresis, but continued to have nocturnal enuresis.

Those children with recurrent urinary infections were controlled, and with the exception of the two with gross anatomic lesions, their infections were completely cured. The two not cured were kept under control with continued antibiotics or chemotherapeutics and periodic urethral dilations.

SUMMARY

A limited series of 19 cases of enuresis in female children, ranging in ages from 3½ to 10 years, has been presented. Seventeen of these children had no developmental defect to explain their enuresis, but all seventeen had endoscopic pathologic findings which were considered worthy of treatment. Two of the children had developmental defects to account for the enuresis. Of these 19 children, fifteen were completely relieved of their enuresis and recurrent infections, four were definitely improved from the treatment as outlined.

CONCLUSION

Local lesions of the urethra, bladder neck, and bladder mucosa are definite etiologic factors in the enuresis seen in female children. By early observation and treatment of these entities, the child and the parents may be relieved of an unfortunate situation, and the future health of the individual may be preserved.

It is believed that many children with enuresis are never seen by a urologist, though they have not responded to other methods of treatment. It is felt that we should be more active in bringing this problem before the profession by calling its attention to undergraduates as well as to our colleagues through our county societies and other organizations.

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Accepted for [illegible]

[1] Herbut, P [illegible] Febiger, 1952

[2] von Recklin[illegible], 1882

CASE REPORTS

Case 1. T. G., a 39 year old white man (BUI 35799), was first admitted to the Brady Urological Institute on October 18, 1944 on the service of Dr. J. A. Campbell Colston with the complaint of low back pain radiating down both legs. There was no history of familial disease. The patient was married and had one child. He had undergone appendectomy at age 28, and at age 32 he was treated medically for an ulcer of the stomach. In a period of 7 years prior to being seen the patient had experienced several attacks of severe renal colic, but no stones were passed nor were calculi demonstrated on repeated radiological examinations.

About three months before coming to the Brady Urological Institute, the patient began to note that erections were weaker, and he began to have some dull, intermittent pain across the back and in the thighs. He consulted a doctor who discovered a rectal mass and advised referral. There had been no difficulties whatever in voiding.

On admission, physical examination revealed the patient to be in good general condition with normal vital signs. The skin showed multiple large brown nevi and subcutaneous soft nodules. Aside from the rectal examination there were no other abnormalities. The prostate at the apex felt normal but at the base the gland ran into an enormous mass extending in a smooth rectal wall as high as the finger could reach. This was markedly indurated and nontender. Urine examination was microscopically negative and culture was sterile, and blood studies were normal. On cystoscopy the instrument was deviated far to the left by an obstruction to the prostatic urethra. A bulge was seen over the right posterolateral wall of the bladder, with some extension to the left side. This was covered with smooth mucous membrane aside from two small cysts on the surface. On bimanual examination the mass was found to be everywhere freely movable. On the plain abdominal x-ray no abnormalities were seen except for a small area of rarefaction in the head of the left femur. On excretory urography both upper and lower tracts appeared normal. With a preoperative diagnosis of possible sarcoma or dermoid, an exploratory laparotomy was carried out by Dr. Colston. The mass was approached transperitoneally through a suprapubic incision, a few peritoneal adhesions to the large and small bowel over the growth being divided. A good line of cleavage was established, the mass enucleated, and the cavity drained with extraperitoneal cigarette drains. Apparently the bladder was entered during the course of dissection for suprapubic urinary leakage developed, but cleared promptly on urethral catheter drainage.

Pathological examination: The mass weighed 377 gm. and was entirely encapsulated, with a hard, rubbery consistency. On section it appeared to be white, glistening, fibrous tissue with a few cysts containing gelatinous fluid. H and E stain showed great masses of fibrous connective tissue in strands and crossing patterns (fig. 1). Scattered areas showed large collections of cells varying in size, shape, nuclear size, and staining characteristics, thought indicative of early sarcomatous change. The growth was compatible with neurofibroma.

The patient was re-admitted in July 1945 for a urinary tract infection. At that time rectal examination revealed some indefinite thickening about the bladder

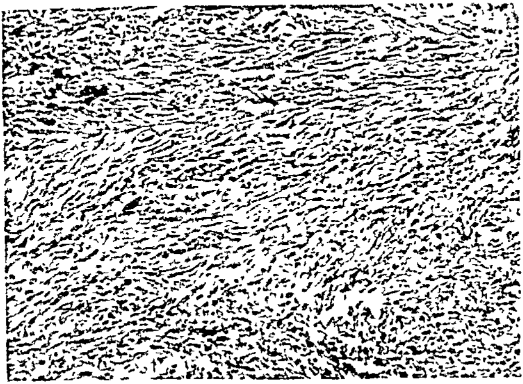

FIG. 1. Case 1. Photomicrograph of tumor showing palisading so characteristic of these growths.

base and seminal vesicles, but no mass or induration could be found. The patient thereafter had vesical and renal calculi removed elsewhere, but a report from Dr. W. L. Bazemore in February 1953 states that he is enjoying excellent general health without evidence of recurrence of the tumor, cutaneous or urinary complications.

Case 2. J. W., a 29 year old Negro (JHH 620601), was first admitted to the Brady Urological Institute on January 15, 1953 for evaluation of a bladder anomaly discovered on routine examination. The family history was negative for skin or other contributory diseases. At age of 5, the patient had undergone operative repair of a valgus deformity of the right foot, and recent x-rays demonstrated partial collapse of the calcaneus and talus. At age of 14, he had umbilical herniorrhaphy. The patient had had no pulmonary complaints, but routine and subsequent chest films showed bilateral apical infiltrations with possible cavitation, repeated cultures for tuberculosis being negative. During 1952, he had typical peptic ulcer symptoms and on December 24, 1952 had a gastro-enterostomy and vagotomy for pyloric and duodenal ulcer. In the course of this laparotomy routine manual palpation in the pelvis revealed a hard, nodular bladder wall. The possibility of multiple diverticula was ruled out by a cystogram (fig. 2, *A*). A cystometrogram indicated normal bladder capacity and pressure relationships. Cystoscopy confirmed the absence of diverticula. The cystoscope was deflected to either side by a firm mass which appeared to lie in the posterosuperior aspect of the bladder between the interureteric ridge and the air bubble. This mass bulged slightly into the bladder. The mucosa overlying it had a velvety hyperemic appearance. No papillary or cystic projections were noted. The remainder of the bladder and trigone appeared uninvolved. Bilateral ureteral catheterization revealed no obstruction in either ureter. Following these studies the patient was transferred to the Brady Urological Institute.

Physical examination revealed normal vital signs in a mentally alert but thin

less there are other similar cases not encountered because not so classified in the literature. Primary bladder neurofibromas appear to originate within the nerve plexuses in the outer muscular wall, producing irregularities of contour without penetrating the mucosal surface. During growth some lie free in the peritoneal cavity and others may become incased within a fibrous capsule from which they may be enucleable. In view of the observation that a good proportion of these cases are completely silent (case 2), presenting no symptoms referable to the urinary tract and in view of the observed tendency to undergo malignant degeneration, we believe it to be absolutely mandatory that all cases of cutaneous neurofibromatosis be subjected to a complete urological survey when the patient presents us with this clinical picture.

Hosoi in a large series of collected cases of von Recklinghausen's disease found that 13 per cent of patients with cutaneous neurofibromas ultimately develop malignant degeneration of tumors, usually in a growth of long duration and manifested clinically by a rapid increase in size. Repeated reports indicate that malignant change apparently follows surgical intervention, and that chances of cure in excision of invasive tumors are small. Neurosarcomas are, in addition, classed as highly radioresistant. Successful treatment seems to depend on the fact that a certain number of bladder neurofibromas are easily resectable or enucleable. It is unfortunate that in only one case is there more than a year's follow-up to indicate the potentialities for recurrence, case 1 presented here having gone over 8 years despite evidence of low grade malignancy at time of removal by enucleation.

SUMMARY

Neurofibromatosis of the urinary bladder should be considered in every case with the cutaneous tumors of von Recklinghausen's disease. Two cases showing low grade malignant degeneration of vesical neurofibromas and treated with surgical excision are presented.

The authors wish to thank Dr. J. A. C. Colston for permission to report his case.

the patterns of the spindle cells. The tumor was very vascular with large, thin-walled vessels. There were rare tumor giant cells and mitoses. Impression was neurogenic sarcoma of low grade malignancy.

DISCUSSION

With the inclusion of these 2 cases of cutaneous neurofibromatosis with bladder involvement there are a total of 16 known cases (tables 1 and 2) with probably 15 biopsy confirmations. Two of this series involved the bladder secondary to a general tumor growth within the pelvic sympathetic nervous system, and doubt-

TABLE 1. *Cases with cutaneous neurofibromatosis*

Gerhardt, C.: D. Arch. f. klin. Med., **21**: 268, 1878.	30 year old male. Multiple small tumors found on vesical neck.
Kyrieleis, A.: Gottingen, 1885.	Pea-sized nodules on surface of bladder. Biopsy?
Steden, E.: D. Ztsch. f. Chir., **177**: 137, 1923.	31 year old female. Suprapubic laparotomy showed the bladder tumor and neurofibroma found in pelvis at autopsy.
Heusch, K.: Ztsch. f. Urol., **21**: 113, 1926.	53 year old male. Small tumors were seen on cystoscopy and diagnosis confirmed at operation.
Heidler, H.: Zentralbl. f. Gynak, **52**: 504, 1928.	68 year old female. Small nodules in bladder on cystoscopy. No biopsy.
Nagahara, Y.: Gann, **34**: 317, 1940.	Autopsy diagnosis of bladder involvement.
Kass, I. H.: Am. J. Dis. Chil., **44**: 1040, 1942.	7 year old male. Suprapubic mass with bladder assymetry on cystogram. Autopsy diagnosis.
Chalkley, T. S. and Bruce, J. W.: J. Pediat., **20**: 632, 1942.	9 year old male. Family history of neurofibromatosis. Suprapubic mass, at biopsy seen to be thickened bladder.
Kimbrough, J. C., Furst, J. N. and Worgan, D. K.: Mil. Surg., **102**: 346, 1948.	29 year old female. Bladder base involvement by two oval masses.

TABLE 2. *Cases without cutaneous neurofibromatosis*

Thompson, G. J. and McDonald, J. R.: J. Urol., **43**: 831, 1940.	59 year old male. Large neurofibroma removed from posterior vesical wall.
Mintz, E. R.: J. Urol., **43**: 268, 1940.	28 year old male. 315 gram, radio-opaque, pedunculated within bladder.
Pitts, H. H.: Urol. & Cutan. Rev., **53**: 623, 1949.	7 year old male Indian. Suprapubic mass infiltrating bladder wall and extending outward. Ureteral obstruction.

Secondary bladder neurofibromatosis

Winestine, F.: J. Cancer Research, **8**: 409, 1924.	60 year old male. Autopsy showing large masses involving abdominal and pelvic nerves, including bladder wall sympathetics. Without cutaneous form.
McDonnell, C. H.: Am. J. Surg., **34**: 90, 1936.	37 year old male. Cirsoid cutaneous neurofibromatosis and infiltration in and about prostate, urethra, bladder, seminal vesicles, and penis. Died in uremia.

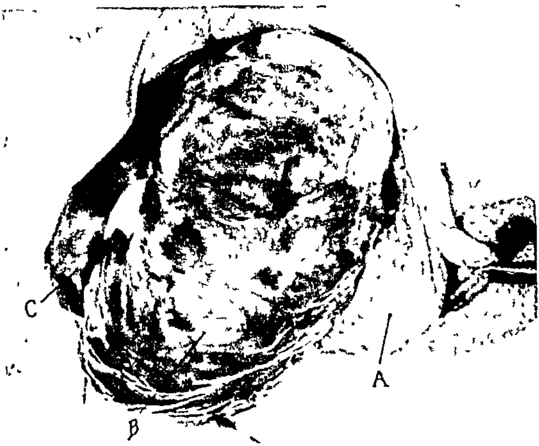

FIG. 3. Case 2 View of tumor at operation *A*, bladder. *B*, tumor *C*, ileum attached at superior aspect of tumor.

in an attempt to free the mass from the bowel. This was closed without difficulty. The bladder defect was closed, a suprapubic tube was placed through an anterior bladder stab wound, and the tumor cavity was drained with a Penrose. Postoperative course was uneventful.

The gross specimen was seen to measure 13 cm. in greatest dimension, and on cut section it contained many cystic areas, localized yellow scarring, and areas of hemorrhage. The microscopic examination (fig. 4) revealed the same changes as seen in the biopsy specimen with areas of loose tissue and poor differentiation of

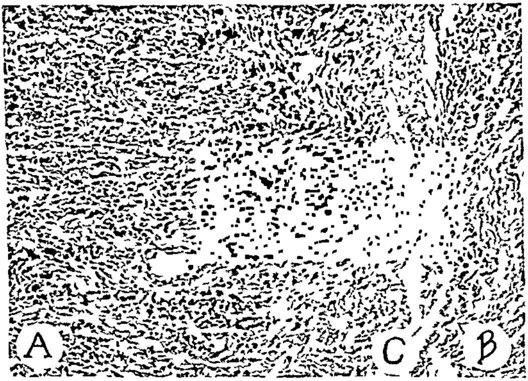

FIG. 4 Case 2 Photomicrograph *A*, tumor. *B*, normal bladder with line of junction, *C*

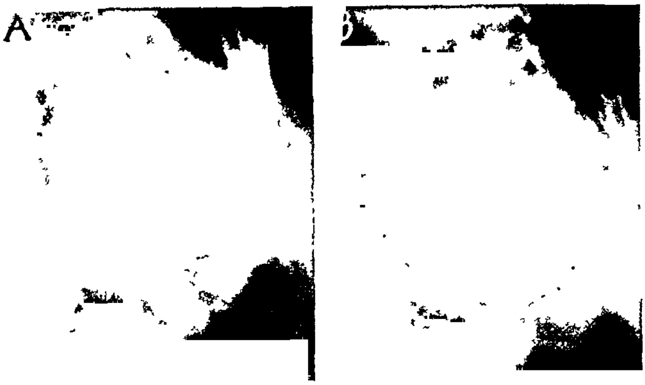

FIG. 2. Case 2. *A*, oblique cystogram 3 weeks prior to operation. No evidence of extrinsic pressure defect. *B*, oblique cystogram taken 1 day before operation. Note pressure defect on bladder.

and chronically ill young man. The skin of the trunk and extremities was covered with *cafe au lait* pigmentations, the largest 8 cm. in diameter, and with very soft subcutaneous nodules of a deep brown or purple color. In the suprapubic area there was an irregular, firm, nontender mass arising from within the pelvis similar to a distended bladder. On rectal examination there was a walnut-sized cystic mass between the rectum and the concavity of the sacrum, with another near the left greater sciatic notch. The prostate was normal. The base of the bladder was thickened and irregular but not hard, a thickened and indurated cord being palpable along the left base. Blood studies were within normal limits and urine examination negative. Excretory urography disclosed normal upper tracts except for a persistent filling defect in the left renal pelvis. Repeat cystogram revealed that the bladder wall still was smooth, but the dome was more markedly depressed (fig. 2, *B*), bearing out the opinion that the mass increased rather rapidly in size in 3 weeks' time. All abdominal films showed a ground-glass appearance within the pelvis with displacement of gas shadows.

Pre-biopsy diagnosis was probable neurofibroma of bladder. A transurethral biopsy of the bladder wall and mass was done, accompanied by extremely free bleeding at the site of excision. Pathological sections showed small spindle-shaped cells arranged in sheets and interlacing strands, with occasional whorls. The diagnosis was neurinoma. Bimanual palpation confirmed the existence of a large tumor occupying the pelvis. This was ballottable and slightly irregular and of a hard rubbery consistency. A week postoperatively an exploratory laparotomy was carried out through a Cherny approach. The tumor was seen to arise from the posterosuperior bladder wall on a broad pedicle and was lying within the pouch of Douglas. The whole surface was covered by peritoneum. On the right superior aspect, a portion of ileum was firmly adherent to it. From its posterior aspect, two thick vascular pedicles could be followed to the internal iliac vessels (fig. 3). The mass was extremely vascular. Attempting to free the pedicle off the bladder wall demonstrated this to be closely integrated with the bladder muscle fiber. The mass was removed by resecting the posterosuperior aspect of the bladder, sectioning and ligating the vascular pedicles. The ileum was opened less there are other similar cases not encountered because not so classified in the literature. Primary bladder neurofibromas appear to originate within the nerve plexuses in the outer muscular wall, producing irregularities of contour without penetrating the mucosal surface. During growth some lie free in the peritoneal cavity and others may become incased within a fibrous capsule from which they may be enucleable. In view of the observation that a good proportion of these cases are completely silent (case 2), presenting no symptoms referable to the urinary tract and in view of the observed tendency to undergo malignant degeneration, we believe it to be absolutely mandatory that all cases of cutaneous neurofibromatosis be subjected to a complete urological survey when the patient presents us with this clinical picture.

Hosoi in a large series of collected cases of von Recklinghausen's disease found that 13 per cent of patients with cutaneous neurofibromas ultimately develop malignant degeneration of tumors, usually in a growth of long duration and manifested clinically by a rapid increase in size. Repeated reports indicate that malignant change apparently follows surgical intervention, and that chances of cure in excision of invasive tumors are small. Neurosarcomas are, in addition, classed as highly radioresistant. Successful treatment seems to depend on the fact that a certain number of bladder neurofibromas are easily resectable or enucleable. It is unfortunate that in only one case is there more than a year's follow-up to indicate the potentialities for recurrence, case 1 presented here having gone over 8 years despite evidence of low grade malignancy at time of removal by enucleation.

SUMMARY

Neurofibromatosis of the urinary bladder should be considered in every case with the cutaneous tumors of von Recklinghausen's disease. Two cases showing low grade malignant degeneration of vesical neurofibromas and treated with surgical excision are presented.

The authors wish to thank Dr. J. A. C. Colston for permission to report his case.

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A DOUBLE PRIMARY CARCINOMA OF THE URINARY BLADDER

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Aside from papillary tumors, multiple primary carcinomas of the genitourinary tract are less common than multiple malignancies elsewhere in the body.[1] To our knowledge not more than 4 previous cases of adenocarcinoma with epidermoid carcinoma of the urinary bladder appear in the English literature and one such unusual case is presented.

CASE REPORT

H. B., a 75-year-old white married man, was admitted to Massachusetts Memorial Hospitals on January 21, 1954, with the chief complaint of gross hematuria of 1 week's duration which increased until the passage of frank blood clots necessitated hospital admission.

The family history revealed the patient's father to have died of carcinoma of the prostate. The environmental history demonstrated a prolonged direct and indirect exposure to aniline dyes. From 1912–1916 he worked in the transportation of drums of aniline dyes, frequently staining his hands with the material. For the succeeding 35 years he worked as a shipper in a leather factory handling skins treated with aniline dyes, although he was not directly active in the processing of the hides.

The physical examination revealed an elderly white man with deafness, a grade I aortic systolic murmur and occasional basilar rales. The remainder of the examination was essentially negative.

The laboratory examinations on admission confirmed the presence of hematuria. There was no anemia and the nonprotein nitrogen was normal.

Roentgen studies presented no evidence of metastatic carcinoma. The flat abdominal film showed both kidneys to be normal in size and shape, and the psoas outlines were clear. Excretory urography showed good dye concentration in the kidneys, with normal filling of the renal pelves and calyces. There was marked irregularity of the bladder consistent with tumor.

On January 22, 1954, cystoscopy revealed a large, fungating, ulcerated growth on the right lateral and posterior wall of the bladder extending to the dome. On January 25, 1954, a partial cystectomy was performed by Dr. Samuel N. Vose. The tumor was found to be a hard, fungating growth involving the entire dome of the bladder, extending into both lateral walls toward the trigone. The lesion was most extensive on the right side, although neither ureter was grossly involved. An estimated three-fifths of the bladder was resected with approximately 1.0 cm. of marginal uninvolved tissue.

This investigation was aided in part by a research grant (C-1754) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

Accepted for publication May 21, 1954.

[1] Kretschmer, H. L.: J. Urol., **40:** 421–445, 1938.

Pathologic study of the resected specimen showed it to consist of a 90 gm. disc-shaped section of urinary bladder and tumor measuring 8.5 by 8.5 cm. in diameter and averaging 3.2 cm. in thickness. The mucosal surface presented a central ulceration measuring 1.6 cm. in cross diameter and 0.3 cm. in depth with tapering margins. The base was granular and a yellowish gray in color. The entire bladder wall was infiltrated and replaced by a yellowish-gray, rubbery, hard tumor which extended to the peritoneal surface and which cut with a granular sensation.

Microscopically a specimen taken from the area of gross ulceration showed the base to be composed, in part, of an elliptical nodule of adenocarcinoma (fig. 1, *A*). The malignant glands were moderately well differentiated and composed of cuboidal and columnar cells with irregular large nuclei. A few mitoses and goblet cells were identified. At its base the adenocarcinoma was surrounding small blood vessels and along one margin it was in contact with but did not merge with typical epidermoid carcinoma, grade II (fig. 1, *B*). At this margin the surface was composed of metaplastic glandular epithelium and there were a few glands of the cystitis glandularis type which did not appear carcinomatous. Beneath the adenocarcinoma, irregular strands of epidermoid carcinoma, grade II, were invading the full thickness of the bladder wall.

An additional section of bladder wall showed the mucosa to be replaced by metaplastic cystitis glandularis (fig. 1, *C*). The cells which formed the glands varied in size, polarity, and nuclear structure, suggesting the possibility of a precancerous condition.

DISCUSSION

Various authors indicate that primary adenocarcinoma of the urinary bladder represents 0.1 to 2.0 per cent of all primary bladder tumors. Howard and Bergman[2] reported 8 cases in 1064 cases of bladder neoplasms, an incidence of 0.75 per cent. Hamm[3] reported 17 cases of glandular tumors of the bladder in a group of 902 cases coded by the American Urological Association Registry of Tumors, an incidence of 1.9 per cent. Coppridge et al.[4] found two such cases listed among 2000 bladder neoplasms coded by the Army Institute of Pathology.

It is generally believed that adenocarcinoma of the urinary bladder arises from one of three possible sites:[5, 6] 1) the paraprostatic glands situated in the bladder neck; 2) urachal rests in the bladder dome; 3) areas of glandular metaplasia anywhere in the bladder, i.e. cystitis glandularis. The latter lesion is considered to be pre-cancerous by many observers.[2, 4, 5, 7] The development of adenocarcinoma in these metaplastic glands is well demonstrated by the present case wherein frank adenocarcinoma is seen adjacent to an area of marked cystitis glandularis.

Multiple primary bladder tumors of different cell origins have rarely been mentioned in the literature. Wagner[8] reported a case of benign adenoma in association with squamous carcinoma in an exstrophied bladder. Mackles et al.[9] described a case of papillary carcinoma with primary leiomyosarcoma of the bladder. Wheeler and Hill[10] described 2 cases of combined epidermoid and adenocarcinoma of the bladder. Saphir and Kurland[11] reported 2 cases in which carcinoma of the urinary bladder contained glandular and transitional cell types, intermixed. They suggested that such tumors arose from one area in which the two cell types were present rather than from two or more separate regions. Because the epidermoid and glandular cells of the tumor herein reported were so sharply demarcated, and because the glandular cells were so clearly associated with marked cystitis glandularis, we consider this case to represent a true instance of double primary neoplasm arising from different cell types and areas.

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[2] Howard, A. H. and Bergman, R. T.: J. Urol., **59**: 455–460, 1948.

[3] Hamm, F. C.: J. Urol., **44**: 227–233, 1944.

[4] Coppridge, W. M., Roberts, L. C. and Culp, D. A.: J. Urol., **65**: 540–549, 1951.

[5] Ash, J. E.: J. Urol., **44**: 135–145, 1944.

[6] Hückel, R.: In Handb. d. Spez. Path. Anat. u. Hist.; Lubarsch u. Henke. Berlin: J. Springer, 1934, vol. 6:2, pp. 632–636.

[7] Patch, F. S.: J.A.M.A., **136**: 824–827, 1948.

Ash[5] found a positive history of aniline dye exposure in 75 of 2500 cases of bladder tumor. Hueper[12] stated that "aniline tumors" of the bladder are usually of the broad based papillary or nodular infiltrative transitional cell type. Although no cases of adenocarcinoma of the bladder in aniline dye workers are previously reported, Hueper stated that "aniline tumors" may be of the glandular type and that they represent 2 per cent of the tumors, an incidence similar to that found in malignant bladder tumors of unknown etiology. He further noted that while most of the tumors occur in workers involved in the processing of aniline dyes, occasional lesions are reported in workers handling the finished dyes.

SUMMARY

A case is reported in which the patient had known exposure to aniline dyes and in whom a separate adenocarcinoma and epidermoid carcinoma of the bladder developed in association with cystitis glandularis. No similar case was found in a review of the literature.

[8] Wagner, A.: Deutsche Ztschr. Chir., 104: 329-334, 1910.

[9] Mackles, A., Immergut, S., Grayzel, D. M. and Cottler, Z. R.: J. Urol., 59: 1121-1126, 1948

[10] Wheeler, J. D. and Hill, W. T.: Cancer, 7: 119-135, 1954.

[11] Saphir, O. and Kurland, S. K.: Urol. & Cutan. Rev., 43: 709-719, 1939.

[12] Hueper, W. C.: Arch. Path., 25: 856-899, 1938.

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THE SURGICAL TREATMENT OF CONGENITAL CHORDEE WITHOUT HYPOSPADIAS

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Congenital chordee without hypospadias is one of the rarest of all genital tract anomalies. Dr. Hugh H. Young in his book, *Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases* (p. 429–431) stated: "As far as we are aware there is no such case report in the literature." Dr. Young treated his case by "cutting the urethra from its anterior connections to completely straighten the penis, thus dislocating the urinary meatus far back almost to the perineum". At a second stage operation a urethra was formed by Young's modification of Tiersche's method.

A similiar case has recently been treated at the University of Michigan Hospital by using a different surgical approach and the successful outcome has prompted the present report.

A 7-year old boy had marked deformity of the penis with a permanent downward curvature. During erection the deformity was greatly increased so that the penis was doubled down upon itself. The urinary meatus was situated in the normal position and the urethra had a normal caliber. The short penile urethra was not attached intimately to underlying structures, and was covered throughout its length by freely movable skin and subcutaneous tissues.

In planning an operative approach (fig. 1, 2, 3) it was considered desirable to preserve the normal distal urethra, rather than laying it open, as Young had done in his technique. Accordingly, a transverse incision was made midway along the undersurface of the phallus, and the urethra was cut across at this point. The urethra was found to lack a corpus spongiosum: it comprised only an epithelial lined tube. Cutting the bow-string permitted complete straightening of the penis without any difficulty, and the cut ends of the urethra were brought to the surface after being "spatulated" in order to insure adequate caliber and to avoid contracture. The transverse skin incision was closed longitudinally and at each end the urethra was sutured to the skin by elliptical anastomosis.

After 6 months the intervening defect was bridged by the performance of a Dennis Brown urethroplasty. The final result is excellent.

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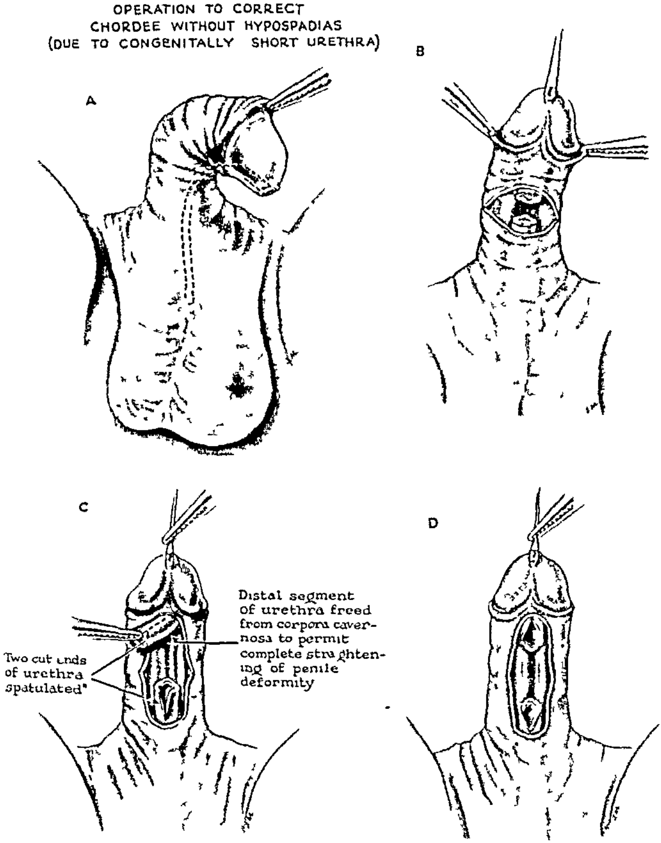
OPERATION TO CORRECT
CHORDEE WITHOUT HYPOSPADIAS
(DUE TO CONGENITALLY SHORT URETHRA)
A
B
C
D
Distal segment of urethra freed from corpora cavernosa to permit complete straightening of penile deformity
Two cut ends of urethra spatulated*

Fig 1

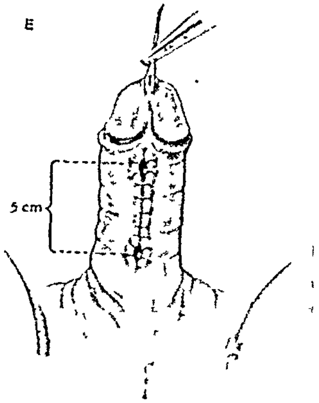

FIG. 2

SECOND STAGE

1-SUPRAPUBIC DRAINAGE OF BLADDER TO DIVERT URINE

2-URETHRAL DEFECT CLOSED BY CONSTRUCTION OF NEW URETHRA, USING DENNIS BROWN TECHNIQUE.

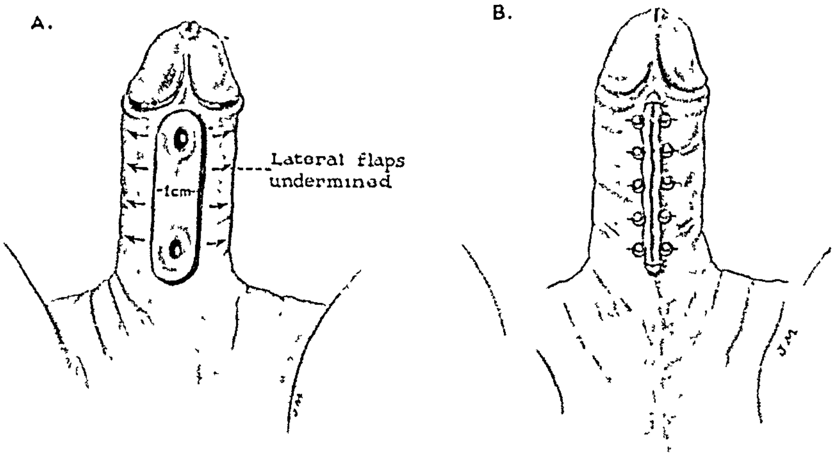

FIG. 3

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PRIMARY CARCINOMA OF THE MALE URETHRA

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Carcinoma of the urethra, although uncommon, is a disease entity which can no longer be considered as an obscure medical rarity A review of the literature discloses a wide divergence in methods of treatment with little exact information about the effectiveness of therapy

McCrea and Furlong[1] recently culled the literature from the year 1834 when Thiaudierre[2] was credited with the first report Approximately 230 proved cases have been tabulated since that time Despite a meticulous survey they were unable to arrive at any decision regarding the value of any specific type of treatment, and were impressed by the paucity and inadequacy of follow-up reports These authors discovered that no patient lived over 10 months from the time of diagnosis without definitive treatment Twenty nine per cent of the recorded cases had either no treatment or simple palliation Penile amputation with regional lymph node dissection was reported only 10 times Accordingly, it would seem appropriate to record the events concerned with 6 male patients who had carcinoma of the urethra and were treated by the two Urological Services of Bellevue Hospital, Second and Fourth Divisions, since 1942

All, save one case, had penile amputations Resection of inguinal or pelvic lymph nodes, or both, was done in four of the patients and cystectomy was likewise performed for two The outcome of the treatments is known in each case

The behavior of carcinoma of the male urethra merits review before considering any form of treatment The lesion is most commonly encountered in the 50 to 70 year age group Paton[3] discovered an 18 year old male who had the disease, while Kroiss reported a case in a man 91 years of age[4] Carcinoma of the urethra, in contradistinction to carcinoma of the penis, is found in all races and men of all major religions, including Jews and Mohammedans[5]

ETIOLOGY

Chronic irritation apparently has a significant etiological role in the development of the tumor, for 48 per cent of the patients were said to have had a coexistent stricture Some of these strictures definitely existed, and had required dilatations prior to the development of the neoplasm The majority of the strictures could be attributed to previous gonococcal infections, while others developed following trauma In some instances the stricture was caused solely by

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Read at annual meeting, American Association of Genito Urinary Surgeons, Absecon, N J June 20, 1952

[1] McCrea, L E and Furlong, J H, Jr Urol Survey, **1** 1, 1951

[2] Thiaudierre P D Bull gen de therap u, p 240, 1834

[3] Paton, W C Indian Med Gazette, **59** 461, 1924

[4] Kroiss Wien klin Wchnschr, **33** 326 1920

[5] Goldstein, A E and Abeshouse, B S Ann Surg, **105** 213, 1937

the actual presence of the carcinoma of the urethra. Various authors include in their case reports other possible etiological factors, such as benign urethral papilloma,[6, 7, 8] chronic nonspecific urethritis,[9] formation of carcinoma in the walls of the fistulous tracts,[10] previous malignant papillary dermatitis (Paget's disease) of the penis,[11, 12] antecedent trauma or other physical or chemical irritants.[6, 13, 14, 15, 16, 17, 18, 19] Still others speculate that the introduction of foreign bodies into the urethra by abnormal sexual compulsion[20, 21] may provoke the tumor. One author advanced the theory that coital contact with female genital carcinoma may account for the lesion in some men.[22]

PATHOLOGY

Metaplasia of the urethral epithelium, incident to chronic irritation and infection, may be the primordial cellular alteration. Various cellular types of carcinoma have been identified in the male urethra. The cancer may consist of transitional cell types similar in character to that of the bladder or may be composed of stratified columnar or pseudo-stratified epithelium such as is normally found in the membranous part of the urethra. The stratified squamous epithelium of the fossa navicularis offers a third type of epithelium potentially capable of undergoing malignant change. The branched tubular mucous glands of Littré, which are lined with columnar cells, may account for adenomatoid structure.[23] Squamous cell carcinoma with its typical central cornification is the type most frequently found, occurring in 70 per cent of the cases. Rarer types, listed in their order of diminishing frequency, are adenocarcinoma, papillary and columnar carcinoma, and transitional cell carcinoma. No case of carcinoid of the male urethra has been reported, although this lesion has been found in the bladder. The early lesion is a well localized growth which later tends to spread by direct extension to involve contiguous tissues. The corpora may harbor the cancer early in the process of growth. Tumors in the deep portion of the urethra may extend to, and invade, the prostate or bladder. Peri-urethral abscess and fistula formation culminating in urinary extravasation result as the process continues. If the growth is located in the distal portion of the urethra it may protrude from the meatal orifice and has been reported to have involved the glans

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[6] Kretschmer, H. L.: Arch. Surg., **6:** 830, 1923.

[7] Grunfeld, J.: Deutsch. Chir., **50:** 193, 1881.

[8] Zaslow, J. and Priestley, J. T.: J. Urol., **58:** 207, 1947.

[9] Guyon, F. and Guiard, F. P.: Ann. d. mal. d. org. gen.-urin., **1:** 513, 1883.

[10] Scholl, A. J. and Braasch, W. F.: Ann. Surg., **76:** 246, 1922.

[11] Tommasoli, P.: Giorn. d. mal. ven., **28:** 542, 1898.

[12] Sequeira, J. H.: Brit. J. Dermatol., **17:** 454, 1905.

[13] Bierberbach, W. D. and Peters, N. N.: J. Urol., **22:** 105, 1929.

[14] Lower, W. E.: Trans. Am. Ass'n. Genito-Urin. Surg., **24:** 249, 1931.

[15] Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926, vol. 2.

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[17] Culver, H. and Forster, N. K.: Surg., Gynec. & Obst., **36:** 473, 1923.

[18] Singer, A. and Dawbarn, R. Y.: Brit. J. Surg., **30:** 280, 1943.

[19] Cuneo and Marcille, M.: Bull. et mem. Soc. d'anat. de Paris, **76:** 671, 1901.

[20] Soubeyran, P.: Bull. et mém. Soc. d'anat. de Paris, **77:** 643, 1902.

[21] Olivier and Clunet. Bull. et mém. Soc. d'anat. de Paris, **82:** 735, 1907.

[22] Selvaggi, G.: arch. ital. de urol., **11:** 487, 1934.

[23] Melicow, M. M.: J. Urol., **54:** 186, 1945.

penis[19, 24] Demonstrable or recognized metastases have been reported in only 15 per cent of the cases recorded in the literature and heretofore were thought to have occurred late in the course of the disease The superficial and deep inguinal nodes are the first lymphatic nodes to be involved Distant metastases to the lungs,[10, 25, 26, 27] pleura,[10] liver,[13, 25, 26, 28] bones,[29] and kidney[14] occur more commonly when the primary lesion is in the posterior portion of the urethra McCrea and Furlong[1] noted that 51 per cent of the tumors were located in the proximal portion of the bulbous urethra, while 11 per cent were located in the pendulous or scrotal segments of the urethra Five per cent were located in both

SYMPTOMS AND DIAGNOSIS

Urethral carcinoma tends to produce a luminal obstruction of the urethra either by its circumferential constriction, or, more commonly, by the intrusion of a pedunculated mass As a consequence, the symptomatology is that of stricture of the urethra A large percentage of the patients are already acquainted with these complaints and are apt to attribute these symptoms to a pre-existing stricture and are not, therefore, alerted to the new danger The caliber of the urinary stream is reduced and there is diminished force of flow which becomes progressively worse, often terminating in complete retention If the tumor is in the anterior urethra and in the pendulous portion of the penis, the presence of a tumor mass located along the urethra or in the corpora may frequently be the first sign that draws the attention of the patient to his trouble[30] Rarely does the growth protrude from the meatus[19, 24] A urethral discharge may occur, and with the proper set of circumstances, may even contain gonococci, thereby masking the more serious lesion[31] Painful priapism and ejaculation may be induced by the invasion of the corpora cavernosa[2] Hematuria is often prominent This is initial in type and is perhaps the most significant of all signs If the foregoing early signs and symptoms are disregarded or erroneously diagnosed, delay may permit peri urethral infection to occur, with induration and abscess formation Fistulas may develop and urinary extravasation may occur with concomitant edema of the penis, scrotum and perineum Early diagnosis is rarely attained, so that the typical sequence of events may be summarized as follows gonococcal urethritis, strictures and difficulty with urination, peri urethral abscess, drainage, fistula formation and, after considerable delay, biopsy and then the diagnosis

The diagnosis of carcinoma of the male urethra is established only by tissue biopsy The palpation of the tumor in the pendulous urethra or in the perineum may alert the examiner to the possibility of a neoplasm, while a carcinoma located in the posterior urethra is obviously more difficult to recognize by palpation

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[24] Gailey H A and Best, J W J Urol , 62 507, 1949

[25] Allenbach, E Deutsche Ztschr f Chir 138 152, 1916

[26] Rinker J R Urol and Cutan Rev , 42 874, 1938

[27] Ideka K Foley, F E B and Rosenow, H J Urol , 49 732 1942

[28] Herger C C and Sauer, H R Urol and Cutan Rev , 46 346, 1942

[29] Robb J J Brit J Surg , 15 605 1928

[30] O'Neil, R F J Urol , 5 325 1926

[31] Kreutzmann, H A R and Colloff, B J A M A 110 184 1938 Also Arch Surg , 39: 513 1939

Urethroscopic inspection and biopsy afford the best promise of an early diagnosis when the lesion is situated near the membranous urethra. The most common error is not to consider the lesion at all. Any stricture which suddenly becomes difficult to dilate and to maintain with an adequate caliber invites the consideration of a malignant lesion of the urethra. A fistula or peri-urethral abscess which does not resolve with usual treatment may be associated with a urethral carcinoma. Other lesions of the urethra and penis to be considered in the differential diagnosis include: peri-urethral abscess, benign papilloma, tuberculosis, intraurethral chancre, gumma, Peyronie's disease, carcinoma of the prostate, or foreign body impacted in the urethra. A case of metastatic carcinoma of the prostate producing a stricture in the penile portion of the urethra has been reported.[18] It is apparent from the medical literature that primary carcinoma of the posterior urethra is rarely diagnosed, or even suspected, before the obstruction demands surgical intervention or fistulas appear that lead to biopsy. At times the diagnosis is made by a biopsy of a metastatic inguinal node. It is to be hoped that routine screening of patients by the study of exfoliated malignant cells in voided urine will result in earlier recognition of carcinoma of the male urethra.

TREATMENT

The treatment of carcinoma of the male urethra is essentially surgical. External radiation is customarily restricted to adjunctive therapy and has been generally regarded as ineffective. The location of the tumor has largely determined the type of treatment selected by most authors. Carcinoma of the anterior urethra has been dealt with by the following methods: partial or complete amputation of the penis, with or without orchiectomy, x-ray treatment of the inguinal nodes, application of radium to the growth, resection of the urethra and the growth, and inguinal adenectomy in conjunction with any of the foregoing.[31] Should the lesion be in the proximal urethra near the bulbous or membranous areas, a more extensive removal is usually considered necessary. This requires divergence of the urinary stream by perineal urethral transplantation. If the corpora cavernosa are involved the entire penis with the crura and the urethra are ordinarily removed.[32] Young described a procedure for the surgical treatment of carcinoma of the bulbous urethra which he termed "both radical and conservative."[33] He advised an excision of the tumor-bearing area including the bulbous and scrotal portions of the urethra along with the three cavernous bodies. The penis was then drawn back into the perineum and the remaining portion of the anterior urethra was anastomosed to the membranous urethra and triangular ligament.

Surgical policy is best predicated on the anatomy of the region and particularly on the related lymphatics. The penile urethra is contained in the corpus spongiosum which runs in a groove between the two corpora cavernosa. Each of the cavernous bodies is enclosed in a fibrous sheath, the tunica albuginea, and all three are encased in a common fascia which is surrounded by subcutaneous tissue and fat. The lymphatics of the penile urethra drain into from one to three

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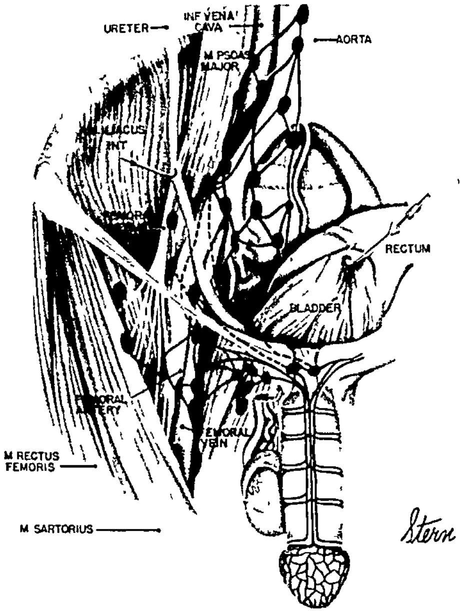
[32] Huggins, C. B. and Curtis, G. M.: Surg., Gynec. and Obst., 48: 544, 1929.

[33] Young, H. H.: Surg., Gynec. & Obst., 68: 77, 1939.



LYMPHATIC PATHWAYS FROM PENIS AND URETHRA

FIG. 1

collecting trunks, which run along the dorsal surface of the penis under the penile fascia and together with the deep dorsal vein (fig. 1). These trunks form a presymphyseal plexus at the suspensory ligament with multiple anastomoses and occasional lymph nodules. From this point the lymphatic trunks divide into three groups; one follows the femoral canal and ends in the deep inguinal nodes; the second, which empties into the retrofemoral nodes, and finally those which follow the inguinal canal adjacent to and accompanying the spermatic cord and finally terminate in the external retrofemoral lymph nodes.[19] It is important to recall that the left and right inguinal lymph nodes have a rich communication with each other through the prepubic subcutaneous lymphatics. The lymphatic drainage from the posterior portions of the urethra is into the deep pelvic lymphatics: the external iliac, the hypogastric and the sacral groups of nodes.[33] Amputation of the penis with dissection and removal of the pre-symphyseal and inguinal nodes is indicated when carcinoma is located in more distal portions of the urethra. Carcinoma of the proximal portion of the urethra, adjacent to the anterior layer of the urogenital diaphragm, implicates the pelvic nodes, and, if an adenectomy is to be considered for a tumor occupying this portion of the urethra, an extirpation of the pelvic lymph nodes is indicated. There is no logical

TABLE 1

Patient	1 J. H.	2 W. B.	3 W. P.	4 E. B.	5 E. N.	6 G. F.
Age	57	43	50	63	71	74
Race	White	Negro	Negro	White	White	Chinese
Gonorrhea	Yes	Yes strictures	Yes strictures	No. Congenital stricture	No	No
Location of tumor	Penoscrotal junction	Distal to bulbous portion of urethra	Bulbous urethra	At penoscrotal junction	At penoscrotal junction	At mid-shaft of penis
Method of diagnosis	Biopsy of periurethral abscess	Biopsy of periurethral abscess	Biopsy of periurethral abscess	Sounds. Biopsy of periurethral abscess.	Biopsy of urethral diverticulum with panendoscope	Biopsy of corpus spongiosum
Pathology	Papillary transitional carcinoma	Adenocarcinoma	Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma	Carcinoma of urethra
Operation	Radical penectomy and amputation of scrotum	1. Local excision and re-anastomosis of urethra 2. Radial penectomy and cystectomy	Radical penectomy and cystectomy Ureterosigmoid anastomosis	Radical penectomy	None	Radical penectomy
Adenectomy	Not done	Pelvic and inguinal nodes	Pelvic nodes	Inguinal nodes	None	Deep and superficial inguinal and pelvic nodes

Radiation	Second to seventh year to lymph-nodes with shrinkage	To lymph nodes with shrinkage	None	None	None	None
Course	Recurrence to perineum and buttocks. Multiple plastic operations.	Progressive deterioration	Rapid weight loss and weakness	Local recurrence	Rapid deterioration	Presently in hospital
Death due to	Carcinoma and myocardial infarction	Widespread metastasis from second primary bronchogenic carcinoma.	Carcinoma and pulmonary embolus	Carcinoma	Carcinoma with inguinal and possible cerebral metastasis	alive
Survival time following diagnosis	Seven years two months	Two and a half years	Two months	Seven months	Three weeks	

rationale for emasculation. In addition to the lymphatics it is probable that the spread of the tumor may be accomplished by way of the blood stream. The metastases of tumor to the lungs, pleura, kidneys, liver, and brain suggest that the lymphatic system alone does not account for such distant spread.

During the 10-year period ending with 1951, there have been 337,397 male admissions to Bellevue Hospital, of which 10,080 were admitted to the urological

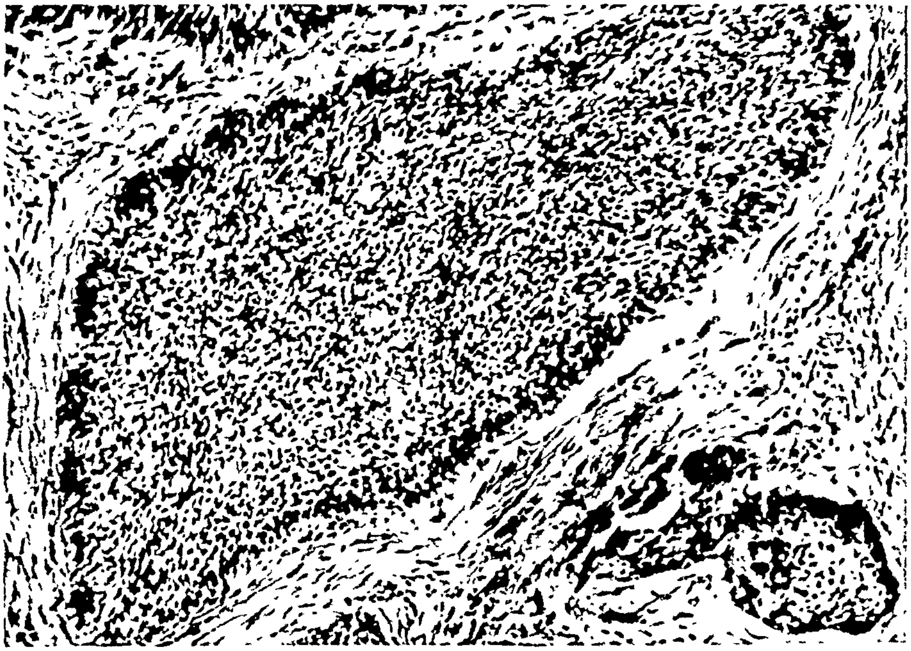


FIG. 2. Case 1. Papillary transitional cell carcinoma. ×180

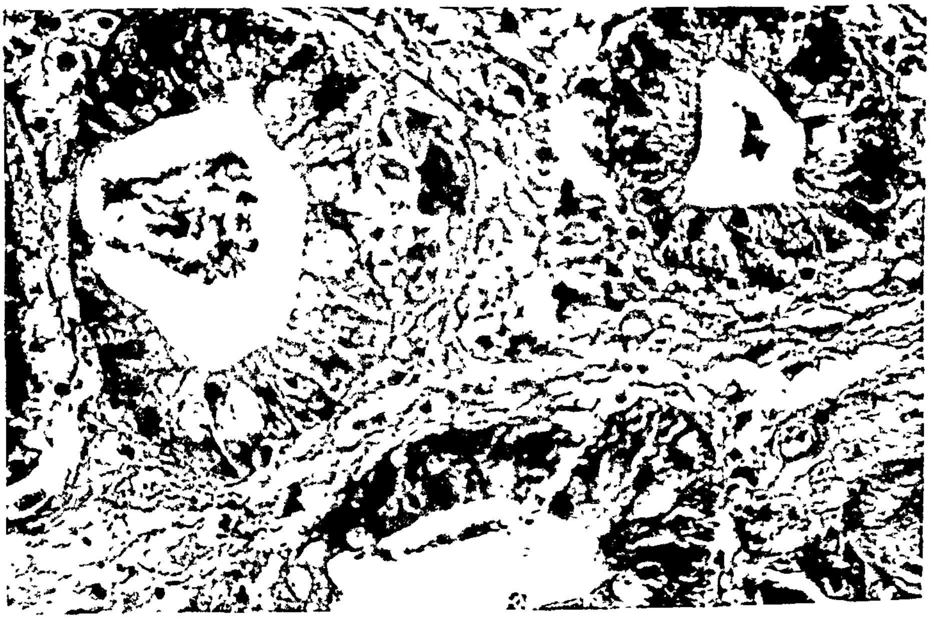


FIG. 3. Case 2. Adenocarcinoma. ×620

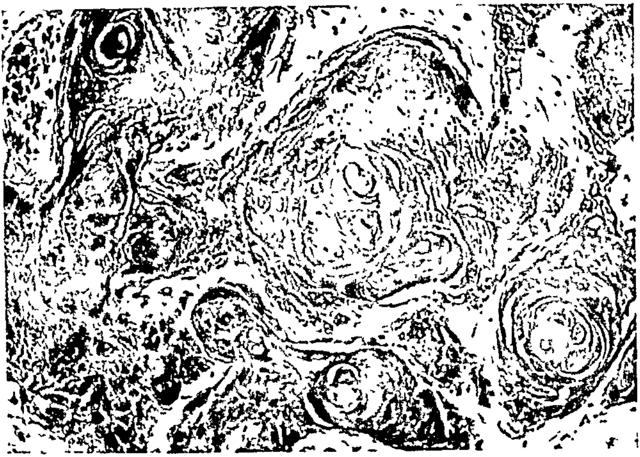


FIG. 4. Case 3. Squamous cell carcinoma with pearl formation. ×200

services. Six cases of carcinoma of the male urethra were treated during this period and are herewith summarized in table 1.* The wide variety of cellular structure of these tumors is illustrated in the accompanying microphotographs (figs. 2, 3, 4, 5, 6, 7).

DISCUSSION

It is apparent from these case studies, as well as from the recorded literature, that carcinoma of the male urethra implies a bad prognosis. Its tendency towards regional recurrence at both the site of the tumor and in the regional lymph nodes compels the surgeon to apply radical means of control if complete extirpation of the tumor is sought. Experience resulting from the foregoing report leads us to the conclusion that early metastasis to the regional lymph nodes may be anticipated. This is in contrast with a generally accepted opinion that metastatic deposits are relatively late as evidenced by the recorded incidence of 15 per cent. Case 6 is informative in this regard. The primary lesion was small in size and the inguinal nodes were not appreciably larger than those encountered in the normal adult. Tumor was found, however, in the nodes when the groin was dissected.

External radiation is held in poor regard by many authors as a means of control. The response to such treatment, as illustrated by cases 1 and 2, would indicate that recurrent tumor was sensitive to radiation as evidenced by temporary resolution of the visible tumors when so treated. Hence such adjunctive treatment might well be employed in such a development.

This review substantiates the necessity for early diagnosis if control is to be gained. The evidence herewith presented suggests that if the tumor progresses

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* Details of the case histories appear in *Transactions of the American Association of Genito-Urinary Surgeons*, 1952

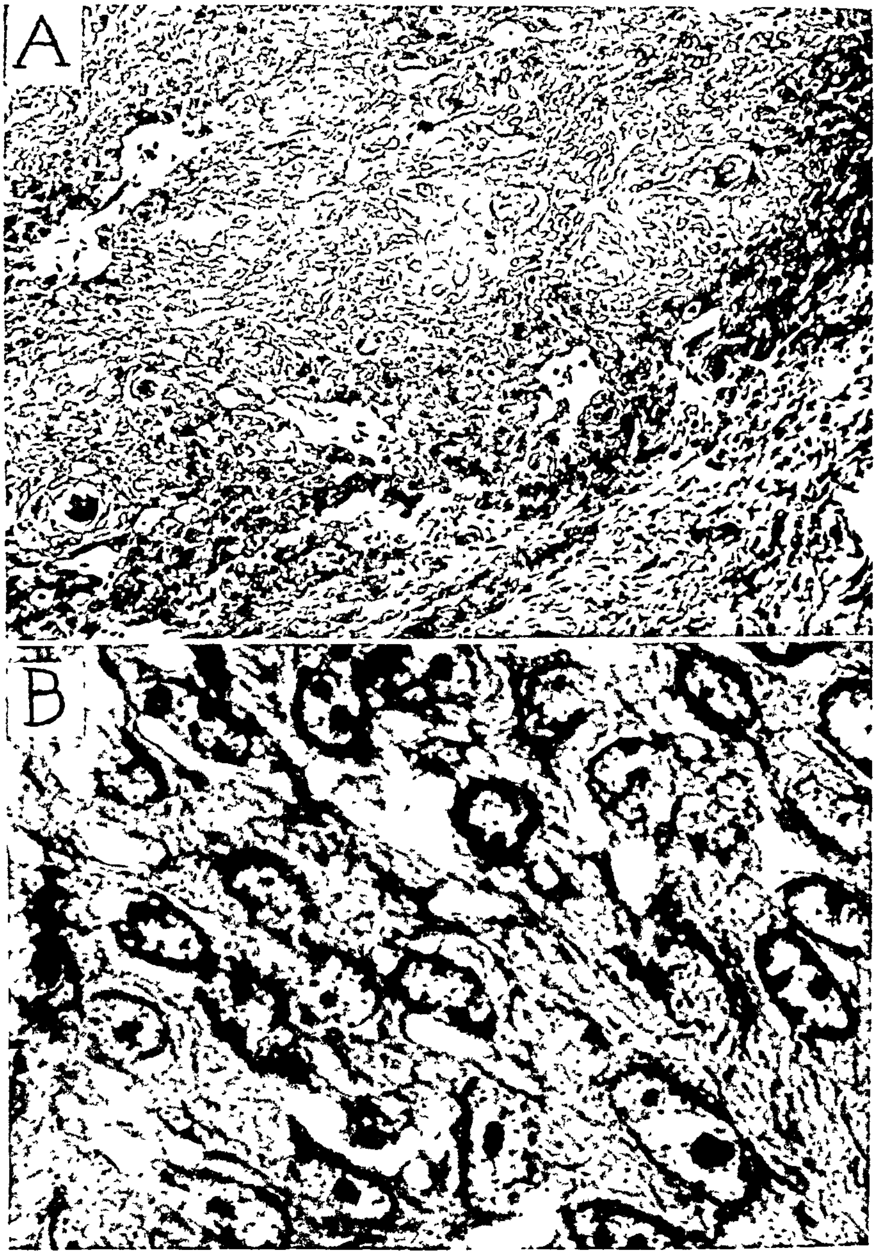

FIG. 5. Case 4. *A*, squamous cell carcinoma. ×90. *B*, mitotic figures seen in higher magnification. ×950

to the stage of peri-urethral abscess the outcome is most apt to be fatal, regardless of the type and extent of the surgery employed. Lesions situated in the pendulous portion of the penis are accessible to early recognition and reasonable hope for cure may be entertained, providing prompt appraisal of the true lesion is made, and appropriate treatment is instituted without delay.

SUMMARY

A discussion of primary carcinoma of the male urethra is presented, the literature on the subject is reviewed, and 6 illustrative cases are reported. Effec-

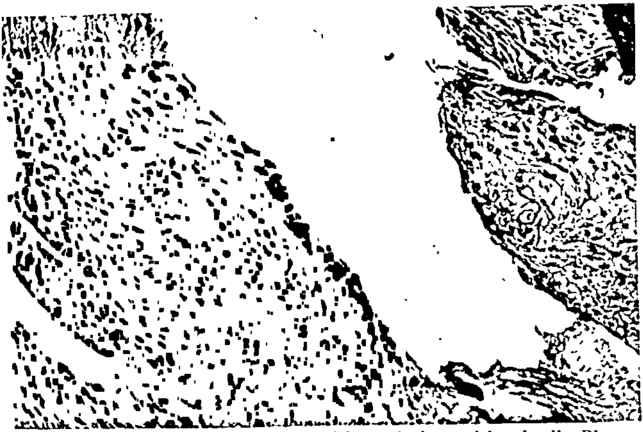

FIG. 6. Case 5. Squamous cell carcinoma with atypical transitional cells. Biopsy of urethra through panendoscope. ×200

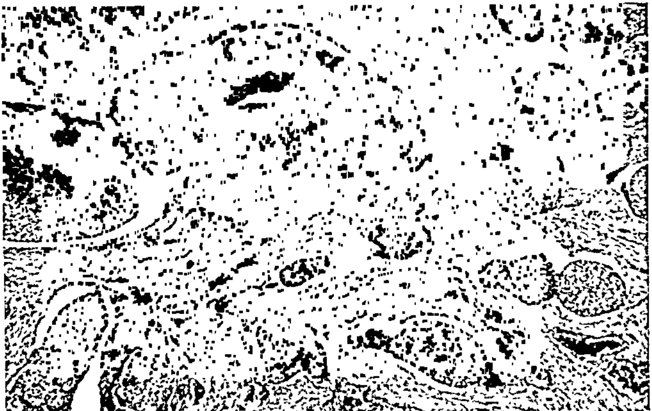

FIG. 7. Case 6. Carcinoma of transitional and squamous types with invasion of lymphatics.

tive control cannot be anticipated unless the lesion is diagnosed at an early stage of its development. That metastasis to the regional nodes may well have occurred regardless of size and routine dissection of the regional lymph nodes, is accordingly indicated.

The authors are indebted to Dr. Sigmund Wilens for his review of the tissue from all the cases and for his comments upon the cytologic structures of the tumors.

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PRIAPISM OCCURRING AS A COMPLICATION OF TULAREMIA

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Although priapism is relatively uncommon, it is frequently due to vascular phenomena when it does occur.[1] Sickle cell disease and leukemia are the most frequently recorded causes of priapsim with secondary thrombotic occlusion of the veins of the penis.[1, 2, 3] So far as we know no case has heretofore been reported in association with tularemia as the causative factor. Recently we have observed a patient in whom priapism developed as a result of vascular occlusion due to severe and fatal systemic tularemia.

CASE REPORT

B. W. J. (W. G. H. No. 40510) a 62 year old white, retired policeman was admitted to the medical service on June 6, 1953. The first diagnosis was pneumonitis of unknown etiology. One week prior to admission, while on a fishing trip in the mountains near Palm Springs, California, a nonproductive cough developed, accompanied by fever, gradually increasing confusion and severe headache. He was seen by his private physician who treated him with penicillin for pneumonia. When the patient failed to respond to treatment he was admitted to the hospital. Previous to this illness he had always been in good health.

Physical examination at the time of admission revealed a confused white man with a temperature of 103.6F. He had evidence of rigidity of his neck. There were moist crepitant rales over the right upper anterior chest and right axilla. The heart was not enlarged. There was a regular rate with an occasional dropped beat. There was mild right upper quadrant guarding of the abdomen but no tenderness.

Laboratory studies at the time of admission were recorded as follows. Blood: white blood count of 4,900 with one metamyelocyte, 35 stabs, 45 mature neutrophils, 10 lymphocytes, 6 monocytes, 3 eosinophils, a hemoglobin of 16.8 grams and adequate platelets. Urinalysis: specific gravity 1.010, albumin 2 plus, sugar negative, and 25–30 coarsely granular casts per low power field. The Klein cardiolipin was negative. A chest x-ray showed pneumonitis of the right upper lobe.

Following admission to the hospital the patient continued to receive penicillin. His temperature became normal on the second hospital day and his mental status improved slightly. A blood count at this time showed 5,200 white blood cells.

On the third hospital day it was noted that the glans penis was markedly swollen, and urological consultation was requested. Despite the patient's con-

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Presented by Doctor Dahlen before the Los Angeles Urological Society, Oct. 6, 1953.

[1] Abeshouse, B. S. and Tankin, L. H.: True priapism; a report of 4 cases and review of the literature. Urol. & Cutan. Rev., **54:** 449, 1950.

[2] Hinman, F.: Priapism. Ann. Surg., **60:** 689, 1914.

[3] Campbell, J. H. and Cummins, S. D.: Priapism in sickle cell anemia. J. Urol., **66:** 697, 1951.

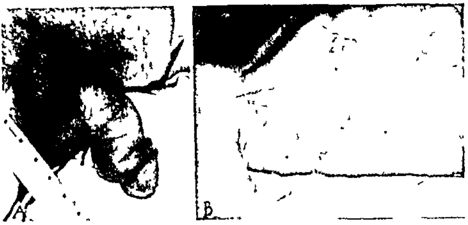

FIG. 1. *A*, priapism of 24 hours' duration. *B*, rash appearing on eleventh day of illness

fusion he was able to deny urinary symptoms. He admitted to having had syphilis in his youth with "treatment" for 6 months. Physical examination revealed a markedly swollen, tender glans penis. It was cool and blue (cyanotic). The corpus cavernosum urethrae was indurated as far posteriorly as the bulb. There was only moderate engorgement of the corpora cavernosa penis (fig. 1, *A*). The scrotal contents were normal. The abdomen was diffusely tender, but no organs or masses could be palpated. Rectal examination of the prostate was not remarkable. Because of the very obvious critical condition of the patient, conservative measures, consisting of an ice bag applied to the penis and sedation, were instituted. A lumbar puncture was performed because of his persistent confusion. During this procedure the patient complained of dizziness and the lumbar puncture was discontinued. The spinal fluid pressure was 80 mm. of spinal fluid and the fluid was bloody. This was felt to be due to the trauma of the procedure.

Laboratory tests on this day revealed 12,200 white blood cells, blood urea nitrogen of 140 mg. per cent and a blood creatinine of 5.2 mg. per cent. Urinalysis revealed no albumin and 3–5 white blood cells per high power field.

On the following day (fourth hospital day) the patient became more stuporous, and his respirations became rapid and deep. His temperature was 101F rectally. The priapism was now more pronounced. Although the patient was able to void through his penis, a urethral catheter was inserted to insure complete drainage of the bladder and to facilitate nursing care. On this day small reddish "spots" about 0.5 cm. in diameter were noted on the chest (fig. 1, *B*). In addition, a shock-like state developed with hypotension (blood pressure 90/70 mm. of Hg.) and cold extremities. An electrocardiogram showed a rapid rate with a wandering pacemaker. The patient was digitalized and in addition he was given noradrenalin intravenously. This raised his blood pressure temporarily. He then became less stuporous.

Blood chemistry studies revealed blood urea nitrogen of 140 mg. per cent, creatinine 5.1 mg. per cent, carbon dioxide combining power of 8.8 mEq, and chlorides of 108 mEq. A blood culture was obtained.

On the fifth hospital day the patient's temperature was 102.4F rectally. He was comatose and continued to be hyperpneic. The "spots" had increased in number and were present on the chest, abdomen, face and thighs. They faded on pressure. The spleen was now palpable. It was noted that the urinary output for the preceding 24 hours was only 500 cc.

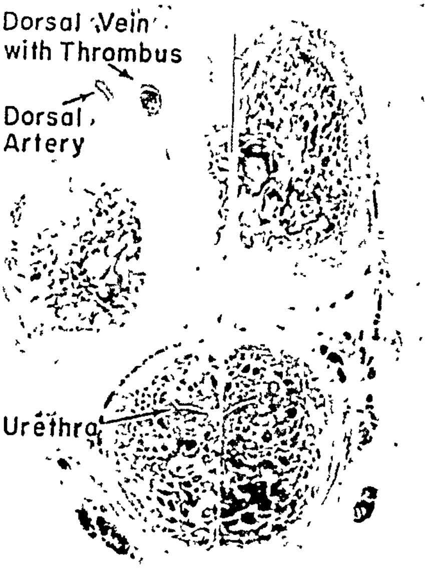

FIG. 2. Cross section of penis distal to bulb

There was no significant change between a chest x-ray taken on this day and the original chest x-ray taken on the day of entry. Blood chemistries revealed a blood urea nitrogen of 144 mg. per cent, creatinine of 5.8 mg. per cent, carbon dioxide combining power 9.6 mEq., and chlorides of 108 mEq. The serum calcium was 8 mg. per cent and phosphorous 7.9 mg. per cent. Agglutination of Proteus strain OX-19 was negative. A Widal agglutination test was negative.

A correct clinical diagnosis was never made.

Because of the lack of response to penicillin, this was discontinued and aureomycin was given. Treatment of his acidosis was continued. The patient continued to be comatose. His left pupil became dilated and irregular, and generalized twitching developed. He ceased breathing and was pronounced dead at 2:30 p.m. on the fifth hospital day (twelfth day of his illness).

A blood culture obtained the day before he died was not reported until after death. It showed Pasteurella tularensis in pure culture. If this organism had been identified before death, or had antibiotics such as streptomycin, aureomycin, or chloromycetin[4-7] been given empirically the patient might have survived.

AUTOPSY REPORT

There were 1500 cc of serosanguineous fluid in each pleural cavity. Irregularly through all lobes were found bronchopneumonic foci. In the right upper lobe these appeared nodular and yellow. Grossly and microscopically they exhibited

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[4] Berson, R. C. and Harwell, A. B.: Streptomycin in the treatment of tularemia. Am. J. Med. Sc., **215:** 243, 1948.

[5] Hamilton, E. L.: A case of pulmonary tularemia treated with aureomycin. New Eng. J. Med., **248:** 1013, 1953.

[6] Woodward, T. E.: Chloromycetin and aureomycin: Therapeutic results. Ann. Int. Med., **31:** 53, 1949.

[7] Parker, R. T., Lister, L. M., Bauer, R. E., Hall, H. E. and Woodward, T. E.: Use of chloramphenicol (chloromycetin) in experimental and human tularemia. J.A.M.A., **143:** 7, 1950.

necrosis reminiscent but definitely not as caseous as tuberculosis The hilar and tracheobronchial lymph nodes were extensively involved by the same process There was neither giant nor epithelioid cell reaction Cultures and stains for tubercle bacilli were negative, however Pasteurella tularensis was isolated Thrombosis of capillaries and both small and large caliber pulmonary veins as a result of the free extension of the necrotizing process into their walls was prominent

Periprostatic and deep pelvic plexus veins showed almost uniform bland thrombosis without mural inflammation This extended through the spermatic veins, dorsal vein of the penis, and through all of the venous structures of the penile corpora (fig 2) The most profound thrombosis was found within the corpus cavernosum urethrae This was associated with infarctive trabecular change Within the corpora cavernosa penis, though extensively thrombosed, there was minimal degenerative trabecular change The subcutaneous venous channels of the penis were likewise thrombosed The dorsal artery of the penis was not occluded Practically no inflammatory reaction, specifically related to this extensive thrombotic process, was observed The testes were hyperemic, but otherwise were normal

This *primary thrombonecrotic pneumonitis* due to Pasteurella tularensis was associated with a septico-pyemia that produced the following anatomic changes foci of necrosis within the liver, spleen, bone marrow and skin nonspecific proliferative glomerulitis, petechial hemorrhages throughout the brain and skin; impending infarction of toes bilaterally, and a terminal invasion of the tracheobronchial tree by Monilia albicans and Aspergillus fumigatus

SUMMARY

Vascular occlusion of penile vessels due to blood dyscrasias is one of the most commonly recognized causes of priapism It may also be due to thrombotic phenomena associated with systemic febrile disease

A case of priapism due to thrombosis of the penile veins secondary to systemic septic infection by Pasteurella tularensis is reported This rare etiology of priapism has not been previously recorded

Patients suffering priapism in association with undiagnosed febrile illness should have immediate blood culture studies as a diagnostic aid

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METASTASIS TO THE PENIS: REPORT OF FOUR CASES

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Involvement of the penis by metastatic cancer is a rare occurrence. Of the 32 reported cases, the cancer originated in the prostate gland in 11, the urinary bladder in 6, and the rectum in 6. In the remaining 9 cases, metastases occurred from tumors arising in the testes, kidneys, lung, liver and ilium.

The reports of secondary cancer of the penis were reviewed by Wattenberg[1] in 1944. He added a case of his own, the sixth reported instance of cancer of the urinary bladder with secondary involvement of the penis. Thompson[2] in 1950 summarized the three earlier reports of involvement of the penis by carcinoma of the rectum, and presented a fourth case. Cattell and Mace[3] in 1951 reported the case of a patient who was living 11 years after abdominal-perineal resection of the rectum for cancer and 9 years after removal of the corpora cavernosum for a solitary metastasis. Bowersox and Frerichs[4] in 1952 reported the sixth case of metastasis to the penis from cancer of the colon. Waller and Hellwig[5] in 1953 summarized all previous reports of metastasis to the corpora cavernosa from carcinoma of the prostate and added one case of their own.

CASE REPORTS

The first two patients were seen for rectal symptoms caused by cancer of the rectum. Metastasis appeared in the penis later.

Case 1. A 51 year old man was first seen in December 1950 with a four year history of passing several loose, occasionally blood-streaked stools daily. A large ulcerated area was felt just inside the anus and a combined abdomino-perineal resection of the rectum was done by Rupert B. Turnbull, Jr., M.D. of the Department of General Surgery. Pathologic examination revealed adenocarcinoma of the anorectum, partly mucinous in type. Intravascular and intralymphatic extension of the tumor and moderate extension of the tumor into the pararectal tissues were found (fig. 1, *A*).

A large right inguinal lymph node was excised in July 1951 and found to contain secondary mucinous adenocarcinoma. A small nodule was then palpable in the corpora of the penis near the penoscrotal junction. For several months the nodule remained the same size, but by March 1952 it had enlarged to several times its original size and was causing difficulty with urination. The patient did not have priapism. The penis was amputated proximal to the nodule and a skin graft was placed around the urethral stump. Pathologic examination revealed secondary mucinous adenocarcinoma of the corpora cavernosa (fig. 1, *B* and 2).

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[1] Wattenberg, C. A.: J. Urol., **52**: 169–175, 1944.
[2] Thompson, H. T.: Surgery, **27**: 216–220, 1950.
[3] Cattell, R. B. and Mace, A. J.: J. A. M. A., **146**: 1230–1231, 1951.
[4] Bowersox, W. A. and Frerichs, J. B.: J. Urol., **68**: 897–902, 1952.
[5] Waller, J. I. and Hellwig, C. A.: J. Urol. **69**: 157–163, 1953.

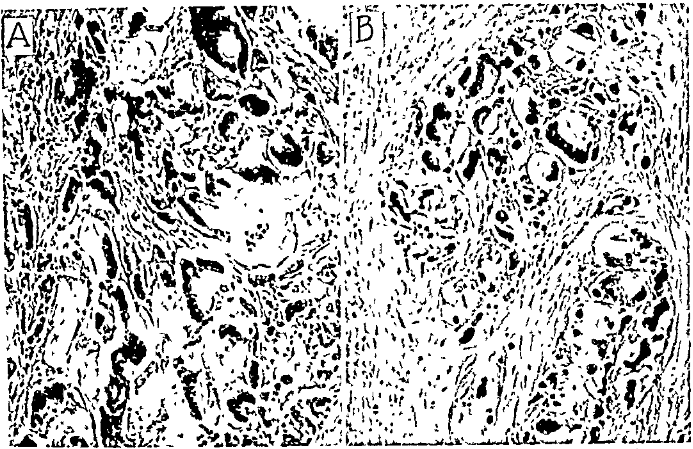

FIG. 1. Case 1. *A*, mucinous adenocarcinoma of rectum. Note presence of mucin around cords of tumor cells. *B*, secondary mucinous adenocarcinoma of penis, similar to primary tumor.

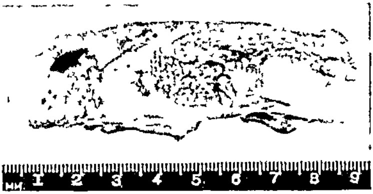

FIG. 2. Case 1. Amputated penis with corpora cavernosa sectioned, showing metastatic tumor near line of amputation.

Subsequently, additional metastases appeared in other parts of the patient's body. He died in July 1952.

Case 2. A 72 year old man was seen in September 1952 because of severe constipation. A large ulcerated neoplasm was found in the rectum two inches above the prostate gland, completely fixed to the surrounding tissues. Biopsy showed adenocarcinoma of the rectum. On laparotomy the patient was found to have extensive liver metastasis and a colostomy was performed by Dr. Turnbull.

Two months later he was having difficulty in voiding, consisting of small stream and nocturia. A nodular area was found in the glans penis about 1 cm. in diameter (fig. 3). Two weeks later a second nodular area was found in the penis and an indwelling urethral catheter was utilized to provide comfort in emptying the bladder. These nodules gradually enlarged to involve the entire glans penis, distal corpora cavernosa, and adjacent skin. Biopsy of the penis revealed secondary undifferentiated carcinoma. The patient died 4 months after the penile metastases were detected.

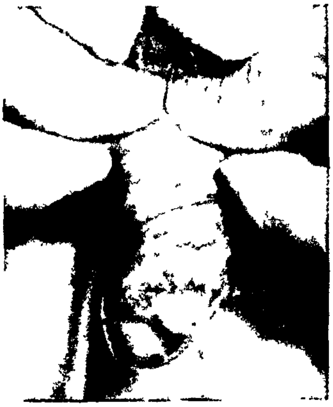

FIG. 3. Case 2. Metastatic tumor nodules close to coronal sulcus in both glans penis and corpora cavernosa.

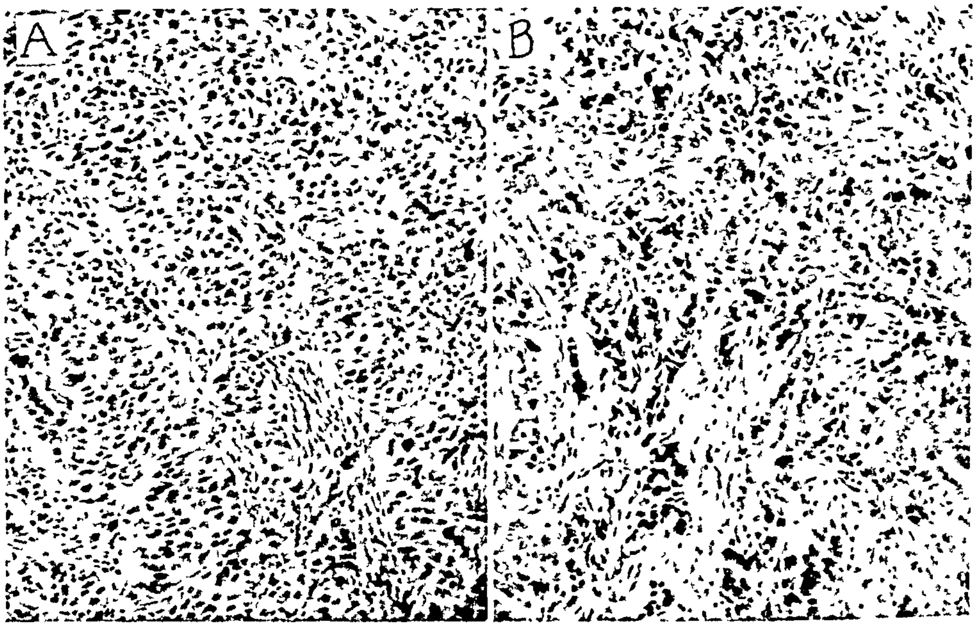

FIG. 4. Case 3. *A*, nonpapillary transitional cell carcinoma of the bladder, squamoid type. *B*, secondary carcinoma of penis.

The next two patients were seen first for urinary symptoms caused by cancer of the bladder. Secondary involvement of the penis appeared later.

Case 3. A 70 year old man was seen in September 1952 with a long history of bladder symptoms consisting of urgency, dysuria and hematuria. A large, hard mass was palpable in the lower abdomen. Rectal examination disclosed a normal prostate and that the mass arose in the bladder, filling the pelvis. Excretory urogram revealed bilateral hydronephrosis and an irregular bladder outline with filling defects.

On cystoscopy the entire bladder was involved by tumor. Biopsy of the bladder revealed a transitional cell carcinoma (fig. 4, *A*) infiltrating the bladder wall. The tumor was considered inoperable and roentgen treatment was administered to the bladder, a total of 12,360 r.

The patient's condition improved; bleeding from the bladder ceased and the

pable. A large benign prostate was evident on rectal examination. The blood urea content was 27 mg. per cent. Plain roentgenogram disclosed multiple areas of calcification within the bladder, consistent with urinary calculi and sand. The excretory urogram disclosed a normal upper urinary tract.

Suprapubic cystotomy revealed a large, hard, tumor mass extending from the bladder neck along the anterior wall of the bladder. Although the tumor had extended through the bladder wall, segmental resection was done. Multiple stones were removed from the bladder and the prostate was enucleated so that the bladder could be closed.

Pathologic examination of the tumor revealed it to be a squamous cell carcinoma of the bladder (fig. 5, *A*). The patient's recovery from operation was uneventful. Two months after operation a hard lump was detected in the corpora cavernosa 2.5 cm. in diameter (fig. 6). Biopsy revealed this to be metastatic squamous cell carcinoma (fig. 5, *B*). A month later the patient died. Autopsy revealed additional secondary carcinoma of the right ventricle of the heart and bronchopneumonia. There was no direct extension of the bladder tumor to the area of secondary carcinoma of the penis.

DISCUSSION

In all four patients, metastatic carcinoma of the penis was detected within a few months after the diagnosis of the primary tumor. Death followed within a short time. None of the patients had priapism, probably because the tumors were present in the distal portion of the penis. Many of the reports in the literature are of patients who had presenting symptoms of either priapism or urinary obstruction. The primary tumor was often discovered later.

It is noteworthy that most of the tumors causing secondary carcinoma of the penis arise from the bladder, prostate gland or rectum. Retrograde flow of blood from the pudendal venous plexus, which communicates with the prostatic and vesical plexuses, to the deep dorsal vein of the penis would explain the presence of metastasis in the penis from these two organs.[6, 7] The rectum is drained by the hemorrhoidal plexuses which form the inferior mesenteric vein. This connects with the portal system. Communications exist between the middle hemorrhoidal vein and the hypogastric vein which receives the drainage of the pudendal and vesical plexuses. Retrograde blood flow, presumably caused by increased intra-abdominal pressure, would permit passage of tumor emboli via this route into the veins of the penis.

SUMMARY

Four cases of secondary involvement of the penis by metastasis from either carcinoma of the bladder or rectum have been presented. All four patients died within a few months of the appearance of the penile metastasis.

Secondary carcinoma of the penis is rare. The probable route of penile metastasis from the bladder, prostate or rectum is by retrograde flow of blood through the pudendal plexus to the deep dorsal vein of the penis.

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CICATRICIAL STENOSIS OF VESICAL NECK AS A COMPLICATION OF RETROPUBIC PROSTATECTOMY

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We have seen several cases of lower urinary tract obstruction in which the patients underwent retropubic prostatectomies at different institutions by several surgeons Inasmuch as we had not observed that complication after other types of prostatectomy, we were prompted to study cicatricial stenosis of the vesical neck following retropubic prostatectomy

If we consider the great number of retropubic prostatectomies which have been done, the frequency of this complication seems to be slight, but we believe that in the future it will be reported more often because it occurs almost always quite late, after the patient is discharged as cured

The mechanism by which this complication is produced is not yet known, various theories have been expounded (heterotopic osteogenesis, infiltration of osteoblastic elements, etc), but in the histologic studies of the fragments removed from our cases only fibrous tissue was found

In reviewing the technique used in handling the vesical neck during retropubic prostatectomy, we were able to observe that the complication is independent of the technique followed

The symptomatology in these cases is typical of vesical neck obstruction Most noticeable is the effort necesary to overcome the obstacle to void The urethral exploration shows a complete blocking of the vesical neck, which does not allow the passage of any of the instruments used Rectal examination shows nothing of note at the prostatic capsule

The panendoscope (fig 1) shows a permeable urethra down to the vesical neck where a fibrous, brilliant, pearl colored septum, typical of a fibrocicatricial process, was found which prevents the passage of instruments to the bladder, in this septum at times a punctiform opening is seen

The x ray eliminates the possibility of calculi or foreign body The injection of an opaque substance permits visualization of the prostatic portion of the urethra and generally a dilatation can be seen which is interpreted as the remains of the prostatic loge (fig 2, *A*) Injecting the opaque liquid at greater pressure, the vesical neck obstruction is overcome and the bladder begins to fill up, which shows the presence of a filiform opening between the urethra and bladder The picture taken after all the cavities have been filled (fig 2, *B*) shows the typical image of this condition where a urethrovesical septum is seen, the cause of the syndrome

Our first idea for relieving the complication was dilatation of the vesical neck with bougies and sounds, but contrary to our expectation we found that instead of relieving the patient the narrowing was made worse and after several days complete retention of urine was produced, which could only be relieved by the use of a Phillips' catheter

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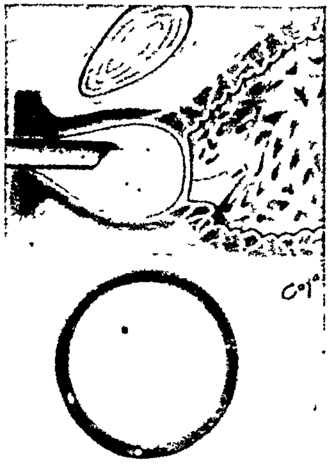


FIG. 1. Endoscopic view of fibrocicatricial septum

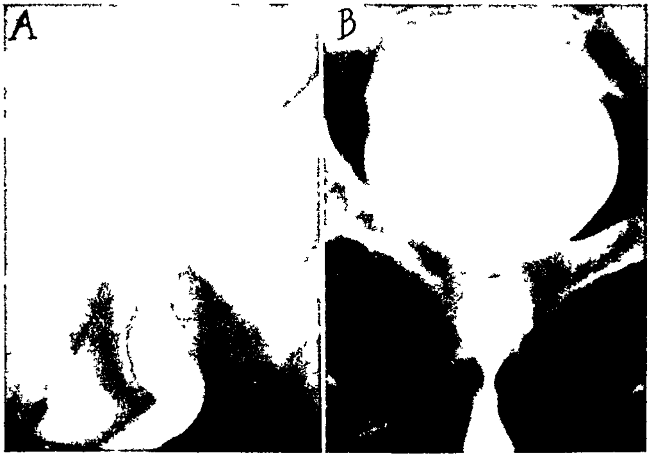


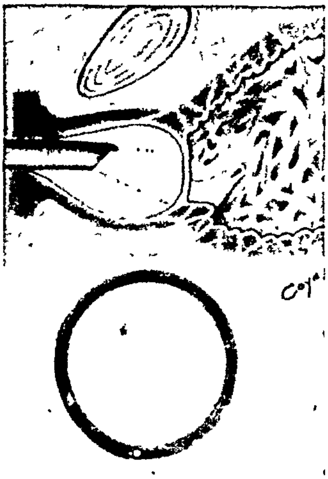
FIG 2. *A*, urethrogram showing dilatation corresponding to prostatic loge. *B*, urethrocystogram showing stenosing urethrovesical septum.

The necessity of an operation upon the bladder neck having been established, one of us (Ajamil), with the panendoscope and Collings' cutting electrode, made an incision on the cicatricial septum and through this opening the resectoscope was introduced (fig. 3).

The postoperative result was so satisfactory (fig. 4) that we decided to use the same technique in all cases in which this complication followed retropubic prostatectomy.

We do not believe suprapubic cystostomy is indicated in this type of case inasmuch as complete recovery follows the aforementioned procedure in a short time.

In accordance with the studies of the antifibroplastic action of cortisone, we have in mind that if in the future similar cases come under our care, we shall use that hormone as an addition to the surgical treatment that we have recommended.



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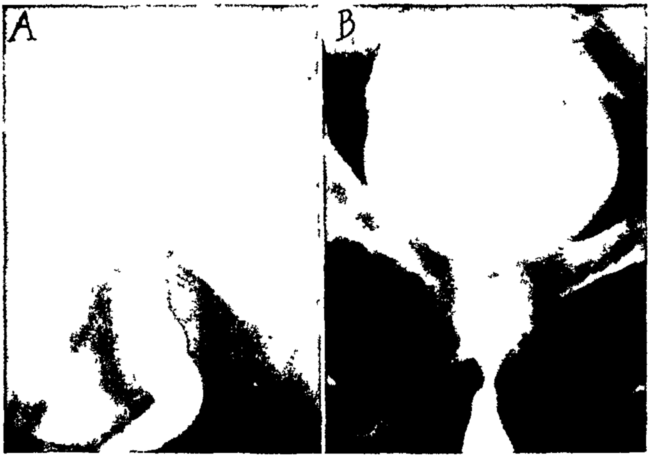

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A CLINICAL STUDY OF BACTEREMIA AND OVERHYDRATION FOLLOWING TRANSURETHRAL RESECTION

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During the course of transurethral resection of the prostate gland and bladder neck, the venous plexus which surrounds the capsule of the gland is often opened, thus offering a ready avenue for the introduction of irrigating fluid directly into the venous system. Following the reports of McLaughlin,[1] Creevy[2] and others, the dangers accompanying the use of distilled water as an irrigating medium have been widely recognized. Investigations of Landsteiner and Finch[3] have shown that as much as 1,000 to 1,500 cc fluid may be forced into the vascular system during the course of a transurethral resection. Vesical and intravascular hemolysis with resultant hemoglobinemia, hemoglobinuria and renal damage has been noted and reported by a number of observers.[4, 5]

We believe it has been definitely established that the use of sterile distilled water for irrigating purposes may cause hemolysis, either within the bladder or the venous system, and, as a result, renal changes of a toxic and obstructive nature may bring about oliguria, anuria and, in rare instances, even death For this reason, we employ a 1.1 per cent glycine solution in all transurethral procedures. This medium was first suggested by Nesbit[6] and has been preferred by us to the use of 4 per cent glucose solution advocated by Creevy.

In addition to the danger of hemolysis and hemoglobinemia, there are two other potentially serious sequelae which may follow the intravenous infusion of irrigating fluid into open venous sinuses in the prostatic bed. These are *bacteremia* and *overhydration.*

During the past 3 years, we have been on the alert to study both possible complications, and these observations comprise the subject of this discussion.

During the years 1951 and 1952, 257 consecutive transurethral prostatic resections were recorded on our service at Wesley Memorial Hospital in Chicago. Of this group, 128 consecutive operative cases were studied with particular reference to the incidence of bacteremia. All of these patients were carefully watched for signs of overhydration during, and especially toward the end of the operative procedure.

Accepted for publication March 17, 1954.

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[4] Goodwin, W. E., Cason, J. F. and Scott, W. W.: Hemoglobinemia and lower nephron nephrosis following transurethral prostatic surgery. J. Urol., 65: 1075-1092, 1951.

[5] Ebert, C. [illegible] the use of glucose and urea in irrigating solutions for transuret [illegible] Urol., 62: 736-741, 1949.

[6] Nesbit, P [illegible] he use of glycine solution as an irrigating medium during transu [illegible] 59: 1212-1216, 1948

TABLE 1. *Complications*

	No	Per Cent
Extravasation of urine (one fatal)	2	0.78
Secondary hemorrhage	7	2.7
Required evacuation and coagulation through the resectoscope	4	
Required catheter drainage	3	
Epididymitis	8	3.1
Urethral stricture	5	1.97
Secondary resection	13	5.1
Thrombophlebitis	2	0.78
Pulmonary embolus	1	0.39
Pneumonia and atelectasis .	1	0 39

TABLE 2. *Associated urinary tract diseases*

Carcinoma of the bladder	17	6.6
Bladder stone	4	1.5
Bladder diverticulum	5	1 9
Prostatic calculi	2	0.78
Tuberculosis of the prostate	2	0.78
Atony of the bladder	4	1.5
Renal calculi	1	0.39

In this group of 257 patients, there was one operative death. This occurred five days after operation and was due to extravasation of urine and cardiac failure. The mortality rate, therefore, was 0.38 per cent for the two-year period. Complications following transurethral resection for the entire period have been carefully compiled in table 1. The associated urinary tract diseases which often complicated the treatment are listed in table 2.

BACTEREMIA AND SEPTICEMIA

Numerous reports in the past have given evidence of the common occurrence of bacteremia and septicemia following manipulation of the prostate and male urethra. Scott,[7] in 1929, reported 82 patients who were found to have bacteremia following various urethral manipulations, and of this group there was a mortality of 18 per cent. In 1930, Barrington and Wright[8] showed bacteremia occurring in a high percentage of patients following urethral dilatation.

Creevy and Feeney[9] recently published a report indicating that 45.4 per cent of patients had positive blood cultures following transurethral resection of the prostate when they had received no preoperative medication. In a comparable group of their patients, the preoperative administration of aureomycin reduced this incidence to 17.4 per cent. Another report of Biorn, Browning and Thompson[10] gave an incidence of 12.3 per cent positive blood cultures occurring postoperatively in a series of 106 patients. No mention is made of preoperative medication. Gray and Scott at Rochester, New York[11] found an incidence of 55.3 per cent positive blood cultures following transurethral resection in a series of 47 patients. Another group of 93 patients subjected to open prostatectomy showed positive blood cultures in 26.8 per cent. All of these patients had received aureomycin for 24 hours preoperatively. There was no evidence in these reports to indicate any increase in morbidity or mortality in those patients who were reported as having had positive blood cultures postoperatively.

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[7] Scott, W. W.: Blood stream infections in urology: A report of 82 cases. J. Urol., **21:** 527–566, 1929.

[8] Barrington, F. J. F. and Wright, H. D.: Bacteremia following operations on the urethra. J. Path. & Bact., **33:** 871–888, 1930.

[9] Creevy, C. D. and Feeney, M. J.: Infection following transurethral resection of prostate gland. Bull. Univ. Minn. Hosp. and Minn. Med. Found., **20:** 311–327, 1949.

Recent reports also have demonstrated the relationship between urologic procedures and subacute bacterial endocarditis. Merritt[12] reports a 10 per cent incidence of bacterial endocarditis following transurethral prostatic resection in patients who had previous valvular heart disease.

We have studied 128 consecutive cases of transurethral resection of the prostate with pre- and postoperative blood cultures taken immediately before and immediately after the operative procedure. Cultures were inoculated within a few hours on enriched tryptose phosphate broth, incubated at 37° for 48 hours. Each day for 3 weeks the broth cultures were subcultured on blood agar plates. A gram stain was made at the same time. Positive cultures were isolated and identified. All preoperative cultures were negative with one exception. This patient showed a positive culture for Staphylococcus aureus on the blood taken before operation, but a negative culture after the procedure. This undoubtedly was due to contamination, and was the only such instance encountered in the group studied. Only two patients in the entire series had a positive postoperative blood culture; an incidence of 1.56 per cent. Both of these patients had a negative preoperative blood culture.

The first patient had received no preoperative medication. The urinalysis showed many leukocytes and a trace of albumin. Following the resection of 25 gm. benign prostatic tissue, his blood culture was positive for Pseudomonas aeruginosa. The temperature rose to 103F on the second postoperative day, and did not return to normal until the fifth postoperative day. This man received gantrisin and terramycin by mouth during the postoperative period. There were no complications and no evidence of any harmful effects as a result of the bacteremia.

The second patient had received preoperative gantrisin and penicillin in therapeutic doses. A preoperative urine culture showed Pseudomonas aeruginosa in heavy growth. Following the resection of 38 gm. benign obstructing prostate, the blood culture was positive with a heavy growth of Pseudomonas aeruginosa. The postoperative course was complicated by epididymitis which appeared on the fourth day and was accompanied by a persistent pyuria which lasted for over three months. This finally responded to intensive chemotherapy and healing of the vesical neck. The postoperative temperature was elevated to 102F and fell to normal on the twelfth postoperative day after continuation of penicillin and gantrisin therapy. The final functional result was very satisfactory in this patient.

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[10] Biorn, C. L., Browning, W. H. and Thompson, L.: Transient bacteremia immediately following transurethral prostatic resection. J. Urol., 63: 155–161, 1950.

[11] Grey, D. N. and Scott, W. W.: The incidence and type of bacteremia at the time of various prostatectomy procedures. Presented at meeting of Clinical Society of Genito-Urinary Surgeons, Rochester, N. Y., Feb. 5, 1953.

[12] Merritt, W. A.: Bacterial endocarditis as a complication of transurethral prostatic resection. J. Urol., 65: 100–107, 1951.

Of the remaining 125 cases in which both pre- and postoperative blood cultures were negative, 67 had received no preoperative medication for control of infection. The others had received sulfa drugs, penicillin, streptomycin or aureomycin or a combination of these agents in the usual therapeutic dosage.

These results offer great contrast to those reported by the other authors cited. The results indicate that in our experience postoperative bacteremia is a rare occurrence, and, when it does occur, is not of any apparent significance. Many of these patients had preoperative urinary infection, and, in some, venous sinuses were entered during the course of the resection so that the possibility of transient bacteremia was certainly present. Most of our patients with severe urinary infection did receive preoperative medication, and this may have lessened the possibility of obtaining a positive postoperative blood culture. However, the discrepancy between the low incidence of bacteremia in the series studied by us as compared to the high incidence noted by others, even in patients who had received preoperative medication, is indeed difficult for us to explain. Our technical and laboratory facilities have been excellent, and in the hands of personnel with an extensive bacteriological experience.

OVERHYDRATION

An occasional complication, not as yet mentioned in the literature, but which we wish to emphasize here, is that of overhydration during transurethral surgery. Prior to this present study, O'Conor and Sokol had observed 4 patients who indicated this additional danger when irrigating fluid was forced through the prostatic plexus during a transurethral resection. Two phenomena were observed. The *first* was the occurrence of acute pulmonary edema in patients undergoing transurethral resections during which considerable venous bleeding was encountered. This was necessarily accompanied by prolonged irrigation and coagulation. The *second* was the observation that there was an output of a very large volume of urine in the immediate postoperative period; usually the day of the operation and throughout the first postoperative day. This occurred despite a normal or restricted intake of fluid during the same period. This had also been noted in patients who had considerable venous sinus bleeding during their operative procedure. It is our belief that these phenomena are due to overhydration from the introduction of large quantities of fluid through the prostatic venous plexus during the surgical period.

Two patients were observed who had sudden left heart failure and acute pulmonary edema toward the end of a transurethral resection. There seemed to be no apparent cause for this sudden development other than overloading of the circulation with irrigating fluid. Two other patients were observed who did not present the above complication, but who were noted to have excessively high

TABLE 3. *Intake and output, case 3*

	Oper Day	1st P. O	2nd P O	3 P O	4th P O
Intake (cc) . .	1800	2554	3020	2400	2700
Output (cc) . . .	3025	4850	2400	1800	2050

TABLE 4. *Intake and output, case 4*

Intake (cc)	3945	3220	2290	2900	2770
Output (cc)	2400	5775	2450	2850	3100

urinary output postoperatively as compared with the fluid intake. None of these patients were in any way edematous before surgery. This discrepancy in output of urine also was considered to be due directly to excretion of fluid from the body following introduction of large amounts through open venous sinuses during the resection. These latter two patients showed no evidence of pulmonary edema during surgery, indicating that they could tolerate excess fluid without circulatory failure. The intake and output records of the latter 2 patients are presented in tables 3 and 4.

In an attempt to determine the incidence of overhydration as well as its degree, we have studied the *pre- and postoperative blood hematocrit levels* immediately before and immediately after transurethral prostatic resection on the same 128 consecutive cases also studied with blood cultures.

Of this group 29 were rejected as unsatisfactory due to clotting or insufficient blood leaving 99 patients with technically satisfactory readings. Sixteen of these showed no change in the hematocrit following transurethral resection. Forty-six patients showed a decrease in the reading ranging from one-half to four per cent and indicating some hemodilution. However 37 patients showed an increase in the hematocrit of ½ to 3 per cent indicating hemoconcentration. There was no correlation between the cases showing hemodilution and the size of the gland or extent of the resection. There were no instances of clinical overhydration observed during the period these hematocrit studies were carried out.

The significance of the hematocrit studies was disappointing and apparently not of any real clinical or laboratory value. More accurate methods of studying blood volume immediately pre- and postoperatively will be necessary in order to evaluate the incidence and importance of overhydration. Further studies using radioactive isotopes to determine blood volume more accurately are contemplated. The possibility of temporary salt-depletion by overhydration is the subject of a present study.

SUMMARY

A group of 257 consecutive transurethral prostatic resections done over a two-year period were studied. One hundred and twenty-eight of these patients were followed in detail with pre- and postoperative blood culture and hematocrit determinations in order to determine the incidence of bacteremia and overhydration.

Bacteremia occurred in only 1.56 per cent of this group and did not seem to offer serious complications. The reason for the discrepancy between this figure and that reported by other authors is not apparent. Preoperative chemotherapy seems indicated in cases with significant urinary tract infections, and in those with valvular heart disease, but not as "routine."

Hematocrit determinations were not sufficiently accurate as a method of estimating blood volume or hemodilution and in this group showed no significant pattern. However our previous clinical observations of overhydration, as manifested by acute pulmonary edema during transurethral resection and unusually large fluid output during the postoperative period, would indicate that more accurate methods of study are needed. Recognition of overhydration is important as cardiac and systemic treatment must be accompanied by withholding additional fluid until proper water balance has become established.

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EFFECT OF NITROFURANTOIN ON BACTERURIA OF INFECTION FOLLOWING PROSTATIC OPERATION

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The purpose of this paper is to present the results of a study of the effect of nitrofurantoin (furadantin*) in the treatment of chronic urinary tract infection. Studies of this agent by Mintzer, Kadison, Schlaes and Felsenfeld[1] revealed that it inhibited many gram negative and gram positive bacterial species *in vitro* in concentrations ranging from 7.3 to 62.7 mcg. per ml. (0.7 to 6 mg. per 100 ml.). Their studies also indicated that the drug was well absorbed after oral administration, and was excreted in urine in concentrations as high as 400 mcg. per ml. (40 mg. per 100 ml.). These investigators, and Norfleet and his associates,[2] found it to be of value in the treatment of infections of the urinary tract in man.

Evaluation of the effectiveness of therapy of urinary tract infection is difficult because of the diverse nature of the infectious lesions, and because of the presence of many factors of noninfectious origin which may modify the course of the disease. In the present study of nitrofurantoin, an effort was made to minimize the influence of these factors in determining the effect of treatment.

This was accomplished by selecting for study chiefly patients with chronic urinary tract infection which had followed prostatic operation. In addition, quantitative as well as qualitative bacteriologic observations on the urine were made, based on a method described earlier in a study of the effect of methenamine mandelate in a similar group of patients.[3]

PLAN OF STUDY

Clinical material. In the study, therapeutic observations were made of the effect of nitrofurantoin in the treatment of 43 patients. Three patients were retreated following recurrence of infection, so that a total of 46 infectious episodes were observed. The 43 patients were all elderly males, of whom 42 had had prostatic operation for prostatic obstruction. The remaining patient had chronic urinary tract infection associated with nephrolithiasis. The patients were followed for the most part on an ambulatory basis in the out-patient department. None

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Aided by grants from Eaton Laboratories, Norwich, New York, Chas. Pfizer & Co., Brooklyn, New York, and Parke, Davis and Company, Detroit, Michigan.

A[illegible] ch 17, 1954.

* [illegible] supplied by Eaton Laboratories, Norwich, N. Y.

[1] [illegible] R., Shales, W. H. and Felsenfeld, Oscar: Treatment of urinary tract infections with a new antibacterial, nitrofurantoin. Antibiotics and Chemotherapy, 3: 151–157, 1953.

[2] Norfleet, C. M., Beamer, P. R. and Carpenter, H. M.: Furadantin in infections of the genito-urinary tract. J. Urol., 70: 113–118, 1953.

[3] Knight, Vernon, Draper, J. W., Brady, E. A. and Attmore, C. A.: Methenamine mandelate: Antimicrobial activity, absorption and excretion. Antibiotics and Chemotherapy, 2: 615–635, 1952.

TABLE 1. *Summary of treatment of 32 cases of urinary tract infection with nitrofurantoin*

Pretreatment Cultures	Cultures during Treatment (2 weeks)			Cultures after Treatment (2 weeks)			Cases Lost from Study
	Bacterial counts (compared with pretreatment)		No growth	Bacterial counts (compared with pretreatment)		No growth	
	No change	Reduced		No change	Reduced		
E. coli (15 cases)	—	1* 6 (new species)	8	2 3 (new species)	6 (all new species)	1	3
Pseudomonas aeruginosa (6 cases)	3	1 1 (new species)	1	1 2 (new species)	—	1	2
Aerobacter aerogenes (5 cases)	3	—	2	2	1 (new species)	—	2
B. proteus (3 cases)	—	—	3	—	2 (new species)	1	—
Paracolon bacillus (1 case)	1 (new species)	—	—	—	1 (new species)	—	—
Str. faecalis (1 case)	—	—	1	—	—	—	1
Unidentified gram neg. bacillus (1 case)	—	—	1	1	—	—	—
Total (32 cases)	7	9	16	11	10	3	8

* Number of cases

clearing of the urine during treatment in 2 cases, and no change in 3. After treatment. 2 continued to have large numbers of Aerobacter aerogenes in the urine, and another had a new species present.

All three patients with Proteus infection in pure culture cleared completely under treatment, although after treatment new species were found in two cases. Paracolon bacillus disappeared from one patient during treatment, to be replaced later by a new species. Streptococcus faecalis was eliminated during treatment in one patient, and an unidentified gram negative bacillus disappeared from one patient, to return after treatment was stopped.

Among this group of 32 patients, new species appeared in the urine of 18 during or after treatment. These new species were principally divided among Corynebacterium sp. (diphtheroids), staphylococci (predominately S. albus), and Ps. aeruginosa. Except for Ps. aeruginosa, the numbers of these new species were never great, and they did not cause severe symptoms.

Thus, in the group of 32 patients with infection caused by a single species, treatment was followed by complete elimination of urine bacteria in 16. Nine patients had urinary bacterial counts reduced, while in seven, pretreatment counts were maintained. In many of the patients, new bacterial species were the cause of bacteruria during or after treatment.

In table 2 are described the results of treatment of 14 cases of mixed bacterial urinary tract infection. In this group, no patient's urine was completely freed

TABLE 2. *Summary of treatment of 14 cases of mixed bacterial urinary tract infection with nitrofurantoin*

Pretreatment Cultures	Cultures during Treatment (2 weeks)			Cultures after Treatment (2 weeks)			Cases Lost from Study
	Bacterial counts (compared with pretreatment)		No growth	Bacterial counts (compared with pretreatment)		No growth	
	No change	Reduced		No change	Reduced		
Pseudomonas aerug., B. proteus et al. (5 cases)	2* (B. proteus eliminated)	3 (B. proteus eliminated)	—	1 2 (B. proteus eliminated)	1 (B. proteus eliminated)	—	1
Pseudomonas aerug., Aerobacter aerogenes (2 cases)	1 (Aerobacter eliminated)	1	—	—	—	—	2
Pseudomonas aerug., E. coli (1 case)	—	1 (Coli eliminated)	—	1	—	—	—
Other mixed infections, including E. coli, B. proteus, Pseudomonas, staphylococci, diphtheroids, paracolon bacillus (6 cases)	4	2	—	2	1	—	3
Total (14 cases)	7	7	0	6	2	0	6

* Number of cases

of bacteria, although the count was reduced in 7 during treatment. Following treatment, there was little further change in the 8 patients observed. It was of interest, however, that in mixed infections which included B. proteus, these species were almost always eliminated, a result which corresponded to the effect of nitrofurantoin against infection with pure cultures of this organism. In contrast, Ps. aeruginosa was rarely eliminated as a component of mixed infection, and, as previously noted, it usually persisted after treatment in patients in which it was the only infecting species.

Therapy of gonococcal urethritis. Three patients with gonococcal urethritis were treated with nitrofurantoin for a period of 72 hours. In one patient the amount of urethral discharge had decreased by the third day of treatment, although gram negative intracellular diplococci were still readily demonstrable in a stained smear of the exudate. In the other two patients, there was no reduction of discharge or other evidence of improvement in the infection.

In view of the little or no improvement, penicillin treatment was begun after 3 days, and within 24 hours the infection in all three patients had completely subsided.

Toxicity and intolerance of nitrofurantoin. Among the 42 patients in whom blood cell counts were made in the course of treatment, eosinophilia in excess of 5 per cent was observed in 17 (41 per cent). No patient's count showed more than 16 per cent eosinophiles, and most were in the range of 6–10 per cent. The eosinophilia was greatest after the second week of treatment, and subsided promptly after treatment was stopped. Three patients with eosinophilia also had a mild, generalized erythematous and exfoliative skin rash. The rash cleared in all three soon after treatment was discontinued. In two of these patients, re-administration of a test dose of nitrofurantoin was followed by re-appearance of the rash. No other signs of hematologic toxicity or allergic manifestations have been observed.

Nausea and vomiting were severe enough in two cases to require stopping treatment, and were present to a lesser degree in two additional patients. In other patients, gastro-intestinal intolerance such as anorexia, nausea, and occasional vomiting caused some difficulty in continuing treatment. Reducing the dose, or giving of milk with doses, diminished these symptoms.

DISCUSSION

In the studies which have been described, the effect of nitrofurantoin has been tested under uniform conditions of treatment and observation in a series of patients, most of whom had urinary tract infection following prostatectomy. Following the start of treatment, there was an abrupt and progressive fall in the number of bacteria which could be cultured from the urine of the 43 patients studied. The median number of bacteria per ml. dropped from several million to a few hundred by the end of the second week of treatment, and at this time more than one-third of the specimens tested were completely free of bacteria. The drug possessed potent activity against strains of E. coli and B. proteus, and was somewhat less effective against A. aerogenes. Infections with Pseudomonas aeruginosa and mixed infections of which this species was a part, responded least well, but in special patients whose mixed infection included B. proteus, this organism disappeared with treatment.

Another phenomenon of interest was that, among the patients whose urine was not cleared of bacteria during or after administration of nitrofurantoin, approximately one-half were caused by new species which appeared in the course of drug therapy or post-treatment observation. These new species were about equally divided among diphtheroids, staphylococci (predominantly S. albus), and Ps. aeruginosa. Although these invaders reached high counts in some specimens, only those containing Pseudomonas strains were associated with any important symptomatology of infection. None of these patients had instruments passed during the period of observation.

The effect of nitrofurantoin in urinary tract infection appears to even greater advantage when it is compared to the urinary antiseptic, methenamine mandelate, which was previously studied by similar techniques.[3] Although it was found that methenamine mandelate was inhibitory against several pathogenic bacterial species, it was quantitatively much less active in the treatment of urinary tract infections than nitrofurantoin. For example, in 61 specimens of urine obtained from 20 patients during treatment with methenamine mandelate, the mean number of bacteria per ml. was approximately 100,000, and no specimens were completely freed of bacteria, although these values represented a significant drop over the pre-treatment counts of the methenamine mandelate treated patients.

Despite the fact that the number of cases treated in which B. proteus was present in the urine was not large, the effect of nitrofurantoin against this organism was most impressive. Since this species is frequently highly resistant to other antimicrobial agents, nitrofurantoin may be of unique value in treatment of B. proteus infections of the urinary tract.

It should be pointed out that none of these patients had bacteremia or systemic manifestations of infection. Since serum concentrations of the drug after usual doses are extremely low, and presumably tissue concentrations are also at this level, it would be logical to expect less benefit from the treatment of systemic infections with this agent.

The eosinophilia observed in this study was not high, and in itself was not considered a contra-indication to treatment. The occurrence of a skin rash in 3 cases did necessitate discontinuance of treatment, although the rashes were not severe. The finding that a small but significant number of patients manifested a sensitivity reaction to the drug (eosinophilia and skin rash) constitutes a warning that this agent should be administered to patients with a history of allergic disorders with the greatest caution, and only under circumstances when other treatment might not be effective.

SUMMARY

Nitrofurantoin has been found to be highly effective in the treatment of chronic urinary tract infection following prostatectomy. Treatment resulted in an abrupt fall in the number of bacteria in the urine, and, in almost one half of the patients, sterile urines were obtained during treatment. The drug was most effective against infections with E. coli and B. proteus.

A moderate eosinophilia occurred in 17 patients (41 per cent), and was associated with a skin rash in 3. Eosinophilia and skin rashes subsided soon after treatment was stopped.

Three patients with gonococcal urethritis were not appreciably benefited in three days of treatment with nitrofurantoin.

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ALLERGIC GRANULOMA OF THE PROSTATE

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Tanner and McDonald[1] first drew attention to a condition known as granulomatous prostatitis in 1943 when they reported 37 cases from the records of the Mayo Clinic. This is a condition in which the prostate gland has the pathological appearance of chronic inflammation as typified by the presence of many histiocytic cells. There is dense infiltration by lymphocytes, plasma cells, large pale-staining mononuclears, polymorphonuclears and eosinophilic cells. Foreign-body giant cells and pseudotubercles are present which may contribute to confusion with tuberculous prostatitis.

In February 1951, Dr. M. M. Melicow[2] presented the first report of a case of allergic granulomas of the prostate gland. His case was characterized by the sudden enlargement of the prostate gland, with resultant vesical neck obstruction. The patient had had asthma for 1 year, and x-rays of the lungs showed lesions suggestive of tuberculosis. There was a high eosinophilia. Pathological examination of the prostate following suprapubic prostatectomy revealed scattered lesions of irregularly, deeply pink-staining areas that were granulomatous in appearance. Under high power examination, these areas were found to be composed of disintegrated connective tissue fibers surrounded by an intense eosinophilic infiltration. Some round cells, plasma cells and lymphocytes were present, along with a few giant cells.

Thompson and Albers[3] in June 1953 presented 32 cases of granulomatous prostatitis. They felt that the case described by Melicow was identical with 2 cases which appeared in their series, and the fact that, clinically, granulomatous prostatitis may easily be confused with carcinoma of the prostate.

We would like to present a fourth case of allergic granulomas of the prostate gland.

Mr. F. S., aged 73, white, case No. 145583, was admitted on the medical service of the Presbyterian Hospital on September 30, 1952 because of frequent episodes of severe dyspnea of 4 months' duration. Previously, the patient had been in good health, working as a policeman until June 1, when these attacks of dyspnea began. He was studied in two other hospitals, where the diagnosis of bronchopneumonia was made, although the diagnosis of pulmonary tuberculosis was first entertained. In addition to dyspnea, the patient also gave a history of urinary frequency, nocturia and difficulty in starting his stream.

The past history was essentially normal.

Urinalysis, complete blood count and blood sugars were normal. There was no eosinophilia.

Read at annual meeting, Mid-Atlantic Section of the American Urological Association, Washington, D. C., April 22, 1954.

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Blood urea nitrogen was 34 mg. per cent.

An electrocardiogram showed right heart strain.

Physical examination showed an emaciated man who was dyspneic and obviously ill. Temperature 98, pulse 100, blood pressure 130/100.

Examination of the lungs showed moist rales at the right base with expiratory wheezes. The percussion note was hyper-resonant.

The heart showed no enlargement. There was a normal sinus rhythm, and no murmurs were present.

The liver's edge was palpable one finger's breadth below the right costal border.

By rectal palpation, the prostate gland was grade 1 enlarged, its consistency that of benign hypertrophy.

The remainder of the examination was normal.

Under medical treatment the patient's condition improved, and cystoscopy was performed on October 6. This revealed 1½ ounces of residual urine, marked trabecular hypertrophy of the bladder, and a large median bar. The patient was placed on constant bladder drainage.

Eight days later, tests revealed adequate renal function.

While on bladder drainage, the patient's general condition improved remarkably, and it was felt by the medical and urological departments that he was a fair operative risk. Therefore, transurethral resection of the median bar was performed on October 22, three weeks after hospital admission. The patient withstood the procedure well, and his postoperative course was uneventful. The pathological description was as follows:

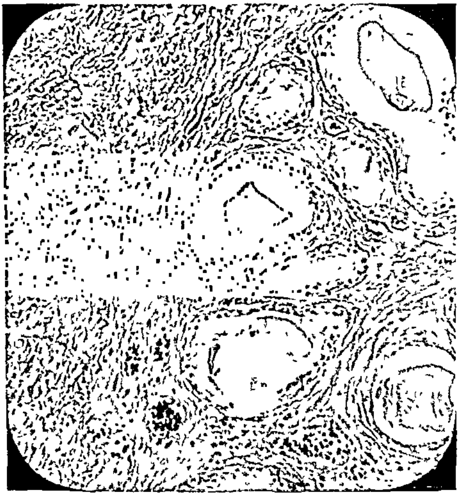

FIG. 1. Section from operative specimen showing benign hypertrophy

Gross description: The specimen consisted of 25–30 fragments of tissue labeled "prostate" averaging about 3 by 5 mm.

Microscopic description: The prostatic fragments displayed varying sized acini usually lined with columnar epithelial cells. Some acini contained inflammatory cells, and the surrounding fibromuscular stroma was occasionally infiltrated.

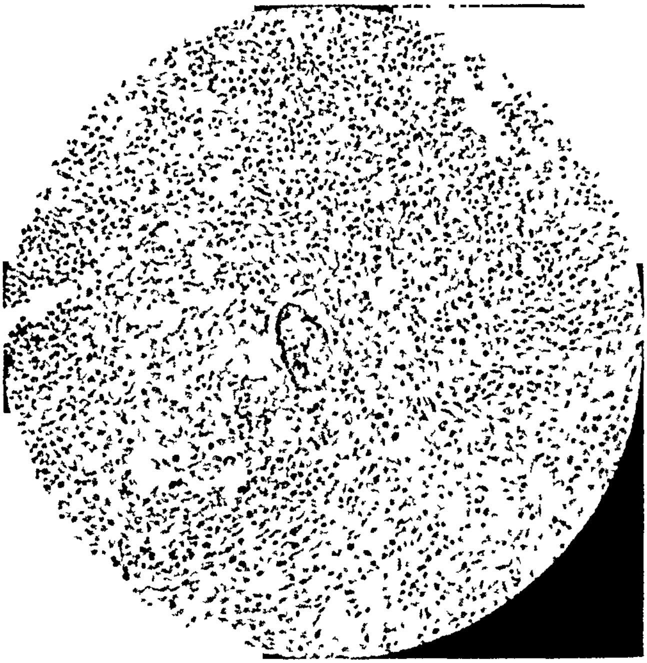

FIG. 2. Section of prostate from autopsy specimen showing area of granuloma

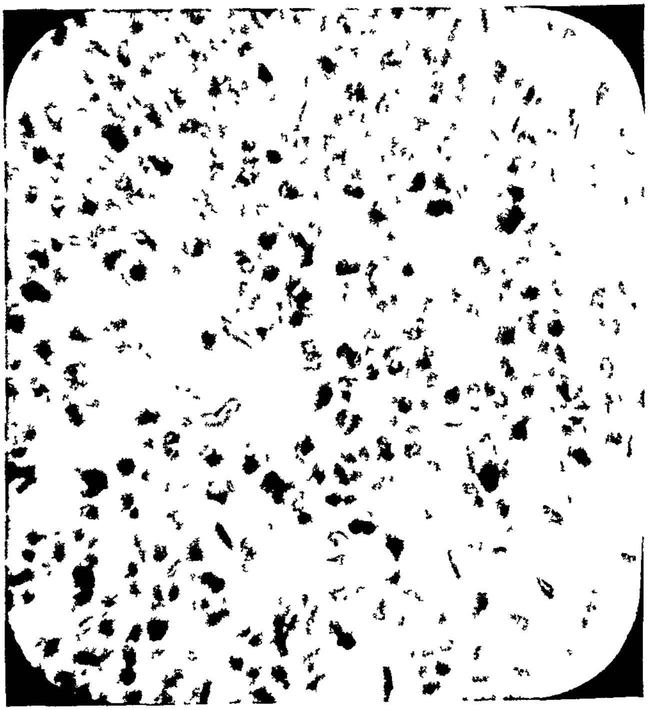

FIG 3. Section of prostate from autopsy specimen showing intense eosinophilic infiltration.

by chronic inflammatory cells. There was no evidence of malignant change in the sections examined.

Pathologic diagnosis: Benign prostatic hypertrophy (fig. 1).

Upon discharge from the hospital, on the eleventh postoperative day, the patient voided comfortably, had nocturia once a night, and no residual urine.

The patient felt well until 3 weeks later when he had a recurrence of dyspnea, wheezing and a hacking cough. He was re-admitted to the hospital on November 29 in critical condition. Measures at management failed, and the patient expired 4 days later.

Autopsy: The lungs showed changes consistent with bronchial asthma and healed tuberculosis. Pulmonary rheumatic heart disease was present. There was an extensive infiltration of eosinophils involving lymph nodes, kidney, liver, bone marrow and prostate. The prostate gland was firm and nodular. Section revealed numerous islands of somewhat cystic yellow tissue of a firm texture and was interpreted as eosinophilic granuloma as described by Dr. Melicow. (See figures 2 and 3.)

DISCUSSION

This condition is of interest to the urologist for several reasons. Clinically the diagnosis of carcinoma of the prostate may be suspected because of the character of the gland on rectal palpation. In two of the 4 cases cited, the preoperative diagnosis was carcinoma of the prostate. In all 4 cases, asthma was one of the principal complaints of the patients. In 2 cases, a marked eosinophilia was present. Furthermore, in these 2 cases, the onset of the symptoms of prostatism was very rapid.

SUMMARY

A case has been presented of a 74 year old white man who had been suffering from asthma for 5 months. Transurethral resection of the prostate was performed because of prostatism. The patient died because of severe bronchial asthma 6 weeks after surgery. Autopsy revealed the presence of so-called allergic granulomas of the prostate.

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PROSTATIC CANCER III. ADVANTAGES OF LARGE ORAL DOSAGE OF DIETHYLSTILBESTROL

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Hormonal control therapy for inoperable, incurable adenocarcinoma of the prostate gland was introduced barely over a decade ago. The opening wedge was made by the advocacy of orchiectomy by Huggins.[1] The "androgen depletion effect" achieved by surgical removal of the testes quickly prompted other investigators to utilize estrogenic substances for the same purpose.[2] Both the natural estrogens and synthetic compounds such as diethylstilbestrol have been employed with little difference in the apparent results.

It now appears that the most valuable form of hormonal control program for prostatic cancer requires immediate bilateral orchiectomy and the institution of estrogen administration.[3] Although orchiectomy is not usually accompanied by distressing undesirable side effects, the untoward reactions from estrogen therapy are sometimes of such severity that the medication must be discontinued.

Most prominent among the undesirable corollary effects of diethylstilbestrol are painful enlargement of the breasts, nausea, vomiting and dependent edema. These are the signs and symptoms that have stimulated a search for a level of estrogen dosage which will minimize or eliminate such reactions.

Originally, and until the present time in most clinics, an oral dosage range of from 1 to 5 mg. of diethylstilbestrol was preferred. In certain patients it has been necessary at this dosage level to discontinue medication because the patient has been unwilling to tolerate the breast pain, nausea and vomiting.

Deming has suggested that a larger dosage of estrogen be employed.[4] His suggestion is for 10 to 15 mg. of stilbestrol daily. This trend toward larger dosage has not received widespread acceptance, but since there is now agreement that estrogens do not demonstrably produce or stimulate cancer in man, perhaps one further objection to larger estrogen dosage has been removed.

The present study was started in 1948 by Fish at the suggestion of Huggins and some of the patients have tolerated these high dosage levels of estrogen since that time, some of them having been given more than a pound of stilbestrol. In large measure it has developed as a result of desperation engendered, in a few situations, by an apparent inability on the part of the prostatic cancer

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patient to tolerate diethylstilbestrol. An attempt to utilize far larger dosage than that usually advised has been made. The early results of this treatment schedule have been interesting enough to prompt this report.

CLINICAL STUDY

A total of 105 patients suffering from carcinoma of the prostate have been treated by a combination of bilateral orchiectomy and massive dosage of diethylstilbestrol. In each case reported here, 500 mg. of this drug have been administered orally, in five 100 mg. tablets daily.

In two instances it has been necessary to discontinue the drug. The incidence of painfully enlarged breasts, of nausea and of vomiting among these 105 patients has been less than 10 per cent. Six cases of pronounced lower extremity edema have occurred, one of which is ascribed to the medication alone, although all were undoubtedly precipitated by it. In several of these 6 patients, either cardiac decompensation or peripheral vascular disease, or both, has been a complicating factor.

In 3 patients, withdrawal of the drug did not relieve the edema, but digitalization did reduce it. In all except one in this group of patients re-institution of 500 mg. stilbestrol daily after digitalization did not produce marked edema again.

The subjective beneficial effects from 500 mg. of diethylstilbestrol daily do not differ in a discernible way from the good results from much lower dosage, either qualitatively or quantitatively, except for one group of patients. In five patients who had become refractory to the effects of low dosage stilbestrol therapy (5 to 25 mg. daily), a second remission in symptoms was induced by the change to 500 mg. In three of these there was objective improvement also. One patient with a large, ulcerating, fistulous mass in the perineum healed after a few weeks' trial on 500 mg. of estrogen daily. In the other two, the local prostatic tumor shrank remarkably, and the osteoblastic distant metastases apparently improved.

One additional impressive observation has been the tolerance of high levels of estrogen in patients intolerant of low dosage. The direct change from low to high levels has been successfully managed several times in this series of cases.

SUMMARY

A group of 105 prostatic cancer patients given 500 mg. of diethylstilbestrol daily is described.

That some patients unable to tolerate low levels of stilbestrol administration are tolerant of high levels is emphasized.

Dependent edema remains a troublesome side reaction with massive doses of diethylstilbestrol.

An additional remission in symptoms is sometimes obtained by a shift from low to high estrogen dosage.

Objective improvement in prostatic cancer has been demonstrated in patients in relapse following, and refractory to, lower doses of diethylstilbestrol.

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PRIMARY ADENOCARCINOMA OF THE EPIDIDYMIS: A CASE OF EMBRYONAL TERATOMA, WITH AUTOPSY FINDINGS

ROBERT COWEN

Reports of primary epididymal neoplasm, consisting of over sixty papers[1] were all of single cases, save those of Thompson[2] and of Hinman.[3]

Testicular tumor classifications[4] are rather confusing, and it is usually recommended that different opinions from experienced pathologists be obtained. Falk and Konwaler[5] report primary tumors of the epididymis as adenomatoid, because of unsatisfactory classifications. Whitehead and Williams[6] report 1 case metastasizing to the lungs, but without autopsy; the primary tumor in the epididymis being indistinguishable from a mixed parotid tumor. Longo, et al.[7] summarize 19 cases, listing two as leiomyomas, and seventeen as adenomas stating that 53 per cent are in this classification. Of 19 cases, eight were preoperatively misdiagnosed as tuberculosis.

There are 134 authentic cases, mostly adenomatoid: Benign primary epididymal tumors were found in 74 per cent; 26 per cent were malignant, and 9 per cent were mistaken for tuberculosis.

The following case of primary teratoma of the epididymis, removed completely by epididymectomy, and misdiagnosed tuberculosis, both preoperatively and microscopically, was treated as such. The patient returned with retroperitoneal metastatic extension; the diagnosis was made by retroperitoneal extra-ureteral deviation.[8]

CASE REPORT

C. J., No. 12074, North Detroit Hospital, was admitted July 5, 1949, with the history of having fallen down stairs, suffering an injured right testicle, with swelling and ecchymoses, which after 2 months, was tapped of 30 cc amber fluid.

A young married man of 29 with a child 22 months old had always been underweight but in good health. There was no family history of tuberculosis. The examination was negative save for a swollen right scrotum with a large hard epididymis and vas; the left was negative. Impression: Epididymitis, right, suspected tuberculosis. An x-ray of the chest (fig. 1, *A*) disclosed faint haziness in the region of the apices. No infiltration was definitely demonstrated and the lungs were otherwise clear. The haziness may be due to pleural thick-

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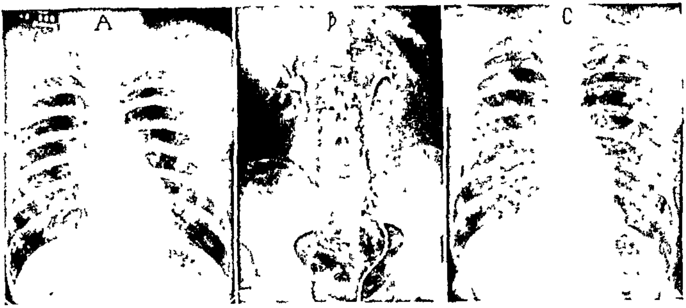

FIG. 1. *A*, chest film taken before epididymectomy for suspected tuberculosis. *B*, retrograde pyelogram 7 months after epididymectomy discloses extra-ureteral retroperitoneal mass. *C*, chest film 7 months after *A*. Massive malignant metastases.

ening. (The patient was advised to have another x-ray of the chest within 3 months.) Impression: Faint haziness in right apex of very mild significance.

Operation, July 6, 1949, right epididymectomy and removal of 30 cc straw-colored fluid; excision of entire tunicae and epididymis with high severance of vas. Diagnosis: Epididymitis, right, tuberculous.

Pathological report: The tunica propria showed a cystic inflammatory area. The epididymis had a small, noninfiltrative, raspberry inflammation. The caput was grossly inflamed, corpus and cauda imbedded in tunical adhesions. The vas was thickened in the proximal portion with the upper vas normal. The epididymis was 2 cm. in its greated dimension and contained numerous small nodular islands of caseous hemorrhagically discolored material. See figure 2, *A*. Microscopic diagnosis: Epididymitis, tuberculous (made because of "giant cells").

Streptomycin was given for 30 days. Healing was clean and the patient was discharged completely recovered.

The patient was re-admitted February 11, 1950. In October 1949 pain and swelling had developed in the right scrotum and subsided under penicillin therapy. He felt well until Christmas 1949, when pain developed in the right groin and back. Chills, fever, and sweating continued for a few weeks but there were no urinary symptoms.

Physical examination was negative save for shotty inguinal glands and tenderness over the right groin. On rectal examination the prostate was golf-ball size with some bulging on the right lateral wall of the rectum. Moderated gynecomastia was present. The impression was right renal tuberculosis.

Cystoscopy (February 5, 1950): Before cystoscopy the diagnosis was right renal tuberculosis; afterwards, retroperitoneal, extra-ureteral neoplasm. The bladder was congested at the outlet with prominent vessels but no suggestion of tuberculosis. Both ureteral orifices were pale and were catheterized easily. Urine from both sides was clear and negative on microscopic examination. Cultures were later reported negative for tuberculosis.

Bilateral retrograde pyelograms (fig. 1, *B*) showed an extravesical tumor on

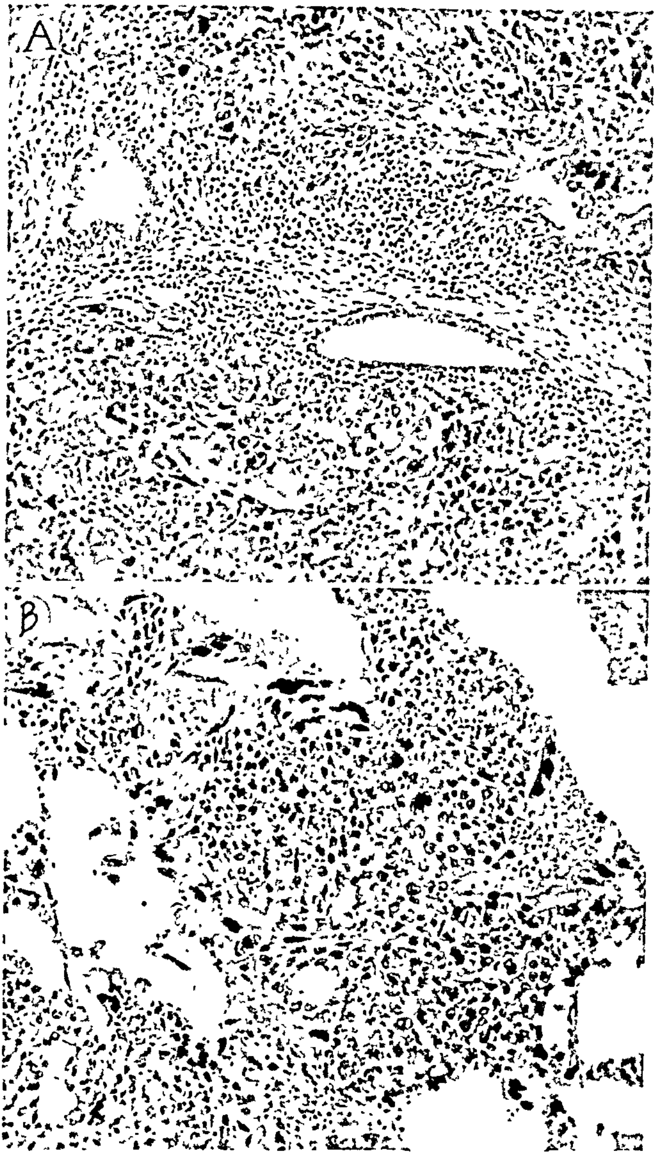

FIG. 2. *A*, mistaken diagnosis of tuberculosis after epididymectomy. *B*, revised examination after finding of metastases.

the right side deviating the ureter medially and involving the horizontal ramus of the pelvic bone. In view of the tuberculous epididymitis, a tuberculous process was not excluded. (P. H. Schraer, M.D.)

Examination of the urine was negative; a culture was negative for tubercle bacilli. Quantitative Aschheim-Zondek, routine positive, 400,000 international units per liter.

A gastro-intestinal series was negative. Re-examination of the chest (fig. 1, *C*) revealed diffuse areas of increased density throughout both lung fields; the appearance of metastatic malignancy. Review of the previous pyelograms showed an area of bone destruction in the right pubic bone. It was noted that Ewing's tumor of the right pubic bone should be considered although the appearance was not typical. Primary sites to be considered were testicular teratoma, hypernephroma or melanoma.

On February 14, 1950 a chest x-ray showed metastatic lesions in both lungs. A low grade fever persisted. The patient's condition was unchanged. He complained of severe frontal headaches; opthalmoscopy negative; it was thought that they might be due to skull metastases. The right testicle was small and of normal consistency; the right epididymis was absent; the left testicle was normal.

Consultation February 27 (Dr. T. Calaghan): Convincing evidence was present of two disease processes: tuberculosis and widespread malignancy, now involving most of the lungs. It was suggested that a tissue review be made for sarcoid. Biopsy of pubis could not be undertaken because of the poor condition. A severe, painful cough developed and the patient expired March 2.

Microscopic report of tissue: The specimen was recognized as epididymis. A small portion remained intact; scattered throughout the rest were many small tubercles containing necrosis and many Langhans type giant cells. The necrosis was not of the caseous type. In these necrotic areas were many large, poorly differentiated cells. The nuclei varied considerably in size, shape, and staining quality. Some were very hyperchromatic and mitotic figures were present. These cells were scattered in small nests and in some areas there was an attempt at glandular or tubular formation. Some of the cells were quite large and had dark pleomorphic nuclei. This lesion was present only in focal areas corresponding to necrotic or destroyed tubules. The tissue between this tubular area was uninvolved by the neoplastic process, but exhibited severe chronic inflammatory reaction. The revised final microscopic diagnosis was 1) embryonal carcinoma containing adenocarcinomatous and trophoblastic elements involving the epididymis and 2) secondary foreign body reaction with tubercle formation, and formation of numerous epithelioid giant cells. See figure 2, *B*.

To summarize, the patient entered the hospital in July 1949 for removal of a small growth on the right epididymis after injury and several weeks of pain and swelling. Histologically it was reported tuberculosis and treated as such, healed completely. He was re-admitted in February 1950 for right lower quadrant pain. Pyelograms showed retroperitoneal extra-ureteral neoplasm and chest x-ray showed metastatic pulmonary malignancy. Review of microscopic section of epididymis showed embryonal carcinoma with trophoblastic elements. Aschheim-Zondek test revealed 400,000 units of anterior pituitary-like hormone per liter of urine, and gynecomastia. The course steadily deteriorated and the patient expired March 2, 1950.

Autopsy findings: No adhesions were found in the pleural cavities each of which contained over 200 cc sanguineous fluid. The entire parenchyma of each lung was almost completely replaced by well demarcated, spherical, hemorrhagic, friable nodules from 1 to 4 cm. in diameter. Almost no air bearing parenchyma remained in either lung. The bronchi contained slightly bloody froth and there was no gross thrombosis of the pulmonary vessels.

The heart was of average size and contour; the epicardium was smooth and

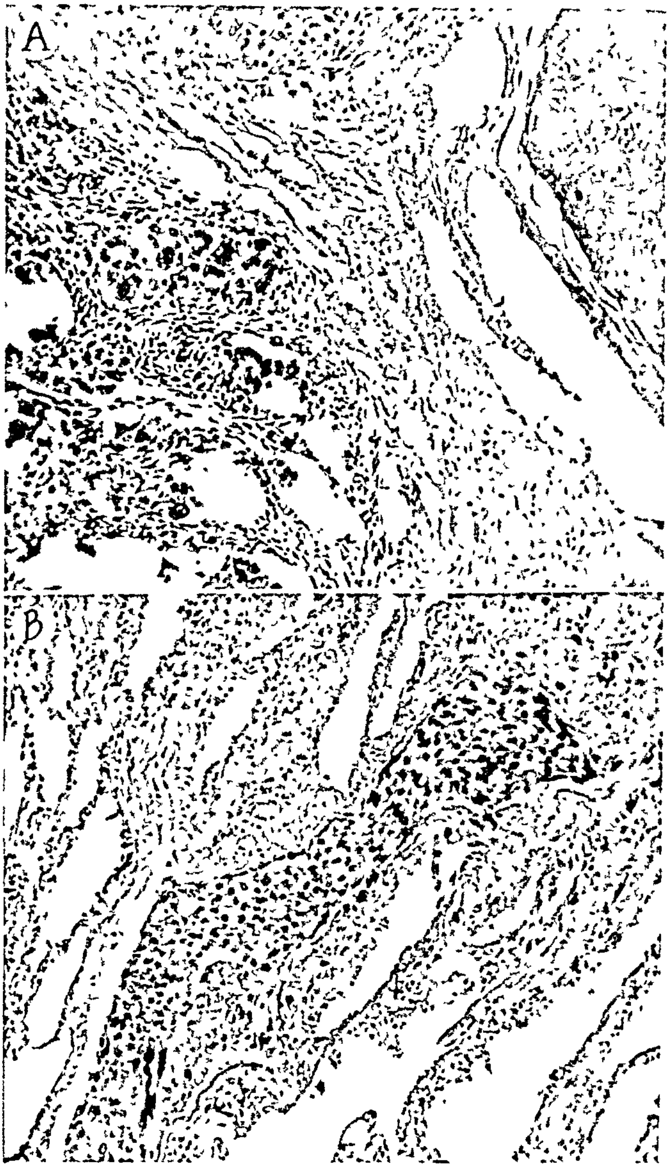

FIG. 3. *A*, cartilage formation in retroperitoneal neoplasm (postmortem). *B*, pulmonary metastasis (postmortem).

the myocardium was homogeneous and pink. The coronary orifices were patent with no atherosclerosis. No gross pathological valve changes were present.

No fluid or adhesions were present in the peritoneal cavity. The liver was at the costal margin and there was no mesenteric lymphadenopathy. The kidneys were of normal weight and configuration. The capsule stripped with ease and on section the appearance was normal.

In the retroperitoneal area, just to the right of the aorta, and proximal to its bifurcation, there was a bilobed smooth mass 3 by 7 cm., composed almost completely of soft, pale, grayish-yellow tissue with the consistency of human brain. In one small area there was well formed cartilage (fig. 3, *A*). Surrounding this area the tissue was extremely friable and hemorrhagically discolored. There appeared to be no involvement of the retroperitoneal lymph nodes.

The bladder appeared normal with no involvement of the prostate gland.

The skin of the scrotum was slightly roughened and scaly. The left testis showed no alteration in the testis, epididymis, or spermatic cord. The right testis measured approximately 4 cm. in diameter. The epididymis was absent and in the region of the epididymis there was a small scar. On section the substance of the testis appeared normal.

Diagnosis: Right retroperitoneal malignant neoplasm, massive metastases in both lungs (fig. 3, *B*), right epididymis surgically removed (residual testis normal).

SUMMARY

The case reported is one of embryonal carcinoma; a teratoma primary in the epididymis. The specimen showed hair follicles and cartilage in the primary and in all the metastatic neoplasms.

The erroneous surgico-pathological report of tuberculosis, the commonest mistake, due to giant cells, resulted in unfortunate delay and postoperative mistreatment. The case was proven primary in the epididymis by the autopsy findings of a normal residual testicle.

The many confusions of classification, and differently diagnosed tumors are frequently due to similarity of malignant giant cells to those of tuberculosis, as well as the frequent clinical impression.

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DIVERTICULUM OF THE VAS DEFERENS: REPORT OF A CASE

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Diverticulum of the vas deferens is a rare condition. Emmerich (1910) and Hinman (1936), after Priesel, illustrate cystic dilatations of the vas deferens occurring near the seminal vesicles. Targett (1890) describes bilateral cystic dilatation of the vas deferens in this area. None of these authors mention the possibility that it may occur in the scrotum.

The present study describes a diverticulum of the vas deferens occurring near the epididymis. The only other similar case was reported by Clarke (1894), who discovered the condition at autopsy.

G. P. (G. H. No. 12356), a 25 year old white man, was admitted to the urological service on March 13, 1950. His chief complaint was gradual swelling of the left side of his scrotum since 1943. At that time he became aware of a scrotal swelling the size of a "small marble" above the left testis. He could not recall any trauma to this area. It was the impression of the patient that while the mass became progressively larger, there was occasional transitory diminution in size. After sexual activity there was tenderness in the mass which was relieved by rest. The only other urological symptom was that of a "strong odor" to his urine.

There was a paternal history of tuberculosis. The past history and system review were negative.

Examination of the genitalia revealed a normal adult penis, right testicle, epididymis, and vas deferens. The left testicle and epididymis were normal. Above the junction of the epididymis and upper pole of the left testis was a tense cystic mass approximately 4 cm. by 9 cm. It was freely movable and did not feel attached to the testicle or to the epididymis. It did not transilluminate.

Laboratory findings including blood Friedman, prolan-A, and pregnanediol were negative.

The clinical impression was spermatocele.

On March 10, 1950 the scrotum was explored and a diverticulum of the left vas deferens was excised (fig. 1). Re-anastomosis of the vas deferens was then performed.

The diverticulum contained a dark brownish-yellow creamy material which, microscopically, contained numerous nonmotile spermatozoa.

The distal vas deferens, leading from the epididymis to the diverticulum, was patent; and it was possible to fill the diverticulum with diodrast (fig. 2). However, the proximal vas deferens was occluded at its junction with the cyst. This obstruction undoubtedly contributed to the formation of the diverticulum.

Externally the wall of the diverticulum showed a fibrotic granular appearance

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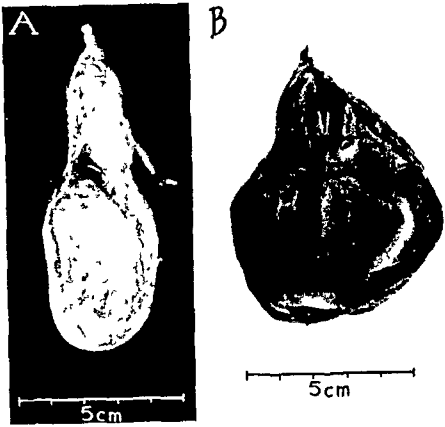

FIG 1

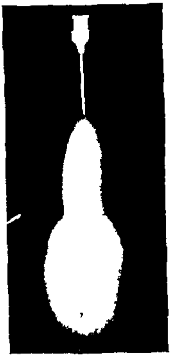

FIG. 2

FIG. 1. *A*, diverticulum of vas deferens *B*, diverticulum of vas deferens opened to show a pin in opening of distal segment of vas deferens

FIG 2. Diverticulum of vas deferens filled with diodrast through distal segment

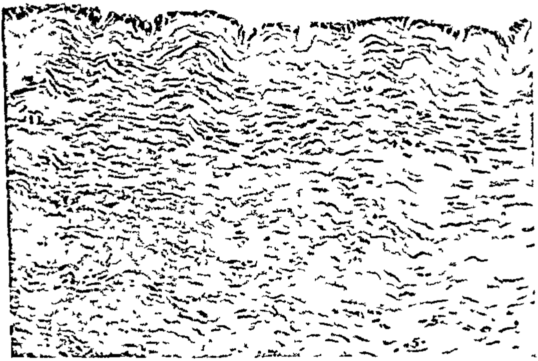

FIG 3 Wall of diverticulum of vas deferens

and a pinkish-grey color. The internal surface of the diverticulum was glistening and smooth, and of a similar color. Microscopically, the diverticulum was found to have an epithelial lining. The wall was fibrous and had developed in close proximity to the vas deferens, the lumen of which appeared to be slightly dilated. The lining of the diverticulum closely resembled that of the vas deferens (fig. 3).

SUMMARY

A case of an unusual anomaly, diverticulum of the vas deferens, is reported.

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CHLOROMYCETIN AND GANTRISIN IN THE TREATMENT OF URINARY INFECTIONS

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Every urologist knows that B proteus is a difficult organism to eradicate from the urinary tract Its incidence has increased since the advent of antibiotics which are potent against the other common invaders of the urinary tract, but which leave B proteus (and usually Pseudomonas aeruginosa) unaffected This gram-negative rod inhabits the normal colon and has, in the past, caused about ten per cent of all urinary infections It is important both because of its resistance to antibiotics, and because many strains can split the urea of the urine to produce ammonia Alkalinization of the urine precipitates the phosphates and carbonates of the alkaline earths, thus leading to the formation of stones It constitutes an especially serious problem when catheters must be left inlying in the bladder, ureter, or kidney, presumably because of contamination of the catheter either directly or through the intermediation of the bed linen (Creevy) Data collected from the literature indicate that 74 per cent of stones associated with infections by urea splitting organisms will recur within three years of lithotomy unless these organisms are eliminated

While infections with B proteus are usually indolent, Scott reported three fatal septicemias following urological procedures Such infections are characterized by septic fever, vascular collapse, nitrogen retention, and a low white blood count

Gantrisin (sulfisoxazol) is said to kill some strains of B proteus Sarnoff was able to control 10 of 14 such infections with this drug, and Haines and Miceli found that blood levels of 10 to 12 mg per cent sufficed to inhibit its growth Carroll has listed the common invaders of the urinary tract in the order of their decreasing sensitivity to gantrisin B proteus, Alcaligenes, E coli, Paracolobactrum, E intermedius, Aerobacter aerogenes, enterococcus, and Pseudomonas aeruginosa Schnitzer has pointed out that the agent is readily soluble at any pH between 6 0 and 7 5, so that crystallinization within the kidneys is not likely to occur While gantrisin is relatively nontoxic, and patients have taken without apparent harm as much as 1650 gm in 90 days (Lazarus and Schwarz), agranulocytosis (Haunz), granulocytopenia (Hagerman), thrombocytopenic purpura (Geiger), and hypoprothrombinemia (Silberg) have been reported, but without fatalities

Chloromycetin (chloramphenicol) was originally extracted from a mould, Streptomyces venezuelae, but is now made by synthesis It is effective against many varieties of organisms, both gram negative and gram-positive Waisbren and Spink have found that B proteus is most sensitive to chloromycetin and to neomycin, although the toxicity of the latter precludes its use except in a dire

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Chloromycetin was furnished by Mr F J Komenda of Parke Davis and Company, and gantrisin by Dr M J Schiffrin of Hoffmann LaRoche, Inc

emergency; the former is said to be sixteen times more effective against the organism than streptomycin.

It was originally believed that the toxic effects of chloromycetin were limited to the production of glossitis, stomatitis, diarrhea, and nausea and vomiting. However, in 1949, Recinos reported several cases of leukopenia after 4 to 5 days of treatment, but observed no serious results. LoPresti saw the leukocytes drop from 17000 to 2800 in eleven days, with prompt recovery with cessation of therapy. Hargraves then reported 9 cases of aplastic anemia after long courses of chloromycetin. Seven of these died within a few hours after the appearance of symptoms. However, no serious reactions have followed short courses of the drug with moderate dosage. It is certainly justifiable to use chloromycetin when a serious infection, or one with serious implications, fails to respond to other drugs.

The use of a combination of gantrisin and chloromycetin seems logical in an effort to eliminate B. proteus, since each one may kill some strains. Herrold and Boand as well as Rhoads have tried this combination.

METHOD OF STUDY

One hundred and nine urological patients have received chloromycetin and gantrisin at the University Hospitals, both because of infections with B. proteus, and with a variety of other organisms which had proved to be resistant to other antibiotics. During the first week the patient received 0.5 gm. of the former and 2 gm. of the latter four times daily. During the second the dose was reduced to 0.25 and 1.0 gm. four times daily; during the third week it was 0.25 gm. of chloromycetin twice daily, and 0.5 gm. of gantrisin four times daily. The urine was cultured before treatment, and again at least a week after the last dose. Minimum urological investigation consisted of an excretory urogram and cystoscopy; predisposing lesions were corrected as far as possible before treatment was begun. The patients were divided into three groups:

1. Resistant chronic infections of the urinary tract.
    A. Due to B. proteus, 39 cases.
    B. Due to other bacteria, 17 cases.
2. Prevention of infection with urea splitting organisms after renal operations requiring the use of nephrostomy or pyelostomy; 14 cases and 35 controls.
3. Prevention of bacteremia and other infections after transurethral prostatic resection; 39 patients. (The investigation was stopped at this point because of the reports of aplastic anemia from chloromycetin.)

Infections with B. proteus (table 1). Of 39 such patients, 28 originally had

TABLE 1. *Results of cultures following treatment*

1. Proteus	6 (16%)	
2. Sterile	13 (33%)	
3. Coagulase negative staphylococci	7 (18%)	
4. Other organisms	13 (33%)	
	39	Proteus eradicated in 33 (84%)

TABLE 2

Organism	Patients Treated	Results of Last Culture
1. Pseudomonas	1	Aerobacter
2. Paracolobacterium	2	E. coli and coagulase negative staphylococci
3. Aerobacter	6	Sterile—1 patient Aerobacter—1 patient Other organisms—4 patients
4. Gamma streptococci	2	Sterile and coagulase negative staphylococci
5. E. coli	2	Both had E. coli
6. Coagulase positive staphylococci	2	Coagulase positive staphylococci and sterile
7. Coagulase negative staphylococci	2	Pseudomonas and sterile

TABLE 3

	Treated with Chloromycetin and Gantrisin	Control
	14 patients	35 patients
Preoperative cultures:		
Proteus	7.2%	21%
Sterile	50.0%	35%
Other organisms	42.8%	44%
Postoperative cultures:		
Proteus	14.0%	35%
Sterile	36.0%	8%
Other organisms	50.0%	57%

predisposing lesions in the lower, 9 in the upper, and 2 in both upper and lower tracts. Twenty-eight were treated surgically, and 27 of these had an inlying catheter for varying periods postoperatively. Eleven had no surgical treatment. The urine was sterilized in 13 or 33⅓ per cent; B. proteus was replaced during treatment with coagulase negative staphylococci (presumably nonpathogenic) in 7 more, and by other organisms ordinarily amenable to other treatment in 13, *so that the B. proteus disappeared as the result of treatment in 33 of 39 patients,* or 84 per cent, an encouraging response.

Infections with other resistant organisms (table 2). This series was incidental to the investigation, and was not pursued when it seemed that little was being accomplished. Sterile urine was achieved in four of 17 patients, but the regimen seemed needlessly stringent considering the organisms involved.

Prophylaxis after renal operations with inlying catheters in the kidney (table 3). Eight of the 14 operations were for renal lithiasis; the others were nearly all Y plasties for noncalculous obstruction at the ureteropelvic junction. Seven and one-fifth per cent had B. proteus in the urine before operation, while 42.8 per cent had other bacteria. The urine was cultured at the time of removal of the nephrostomy or pyelostomy; it was sterile in 36 per cent, and contained bacteria in

74 per cent; Proteus was present in 14 per cent of the postoperative cultures, i.e., the number of infections with B. proteus doubled despite the medication.

For purposes of control, a series of 35 consecutive patients having renal operations with nephrostomy or pyelostomy was studied. All of these received antibiotics other than chloromycetin and gantrisin. Twenty-one per cent had B. proteus before operation; this percentage increased by only one third at the end of the period, so that it was evident that the combination under trial had no value in keeping the organism out of the kidney while a catheter was present, although it seemed to yield a higher overall percentage of sterile cultures than did the other agents (36 as compared to 8 per cent). One can only conclude that the series is too small.

Use in transurethral resection (table 4). Thirty nine patients having 49 transurethral prostatic resections were studied. The urine was cultured before operation and at the time of removal of the catheter on the third postoperative day. The blood was cultured at the end of operation. The patients received 2 gm. gantrisin and 0.5 gm. chloromycetin on the evening before operation and 1 gm. gantrisin and 0.25 gm. chloromycetin 4 times daily for four days postoperatively. Since pyuria and bacteriuria commonly persist for 8 to 12 weeks after operation, we have studied the preoperative cultures of the urine, the postoperative cultures of the blood, and the number and degree of febrile reactions. Fever followed 14 (28.5 per cent) of the operations, but exceeded 103F in but one patient. Convalescence was afebrile in 71.5 per cent. Transitory bacteremia followed 12 operations (24.5 per cent), but there were no severe reactions (above 103F) in this group, although 3 patients had temperatures below 102.8F.

Creevy and Feeney studied the effect of various chemotherapeutic agents upon the incidence of infection after prostatic resection (table 4). Forty-five and seven-tenths per cent of 99 consecutive patients who received no such agents had positive blood cultures. This was appreciably reduced by the use of the wide spectrum agents, aureomycin being the most effective in this regard, as well as in reducing the occurrence of fever.

TABLE 4

Series	temperature to 102.8F	temperature 103F or above	Positive Blood Cultures
1. Control	32.0%	9.0%	45.7%
2. Penicillin	34.4	15.5	41.3
3. Penicillin-sulfadiazine	40.9	20.4	53.2
4. Penicillin-streptomycin	45.4	8.0	39.7
5. Penicillin-streptomycin-sulfadiazine	23.3	13.3	34.5
6. Triple sulfonamide	47.8	13.1	60.9
7. Gantrisin	29.0	6.5	23.4
8. Chloromycetin	34.3	5.5	31.2
9. Aureomycin	25.6	1.6	17.4
10. Terramycin	23.4	2.6	20.8
11. Chloromycetin-gantrisin	26.5	2.0	24.5

SUMMARY

B. proteus is a dangerous infection in the urinary tract, since it predisposes to stone formation. A combination of chloromycetin and gantrisin eradicated 84 per cent of 39 urinary infections due to B. proteus, and it also appreciably reduced the incidence of infection following transurethral prostatic resection. The combination offered little protection against postoperative B. proteus kidney infections where an inlying catheter was present.

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THE TREATMENT OF NONSPECIFIC INFECTIONS OF THE URINARY TRACT

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This discussion does not concern itself with the management of acute transient bacilluria or cocciuria. It is my intention, rather, to discuss 1) the treatment of infections of the blood stream and heart which occur as a result of infection originating in the urinary tract and 2) the treatment of infections of the urinary tract which occur as a result of primary systemic infections, hereafter referred to as localized infections of the urinary tract.

Therefore, the first part of the discussion concerns the treatment of bacteremia and subacute bacterial endocarditis complicating infections of the urinary tract.

BACTEREMIA

The successful treatment of bacteremia depends upon several factors: 1) early recognition, 2) knowledge of the sensitivity of the organism to the chemotherapeutic agent, 3) adequate treatment, 4) removal of foci, and 5) duration of treatment.

Bacteremia due to organisms of the coliform group. Best results will be obtained in the treatment of bacteremia caused by Escherichia coli or the paracolon bacilli if combined therapy is employed (table 1). The method of choice consists of the simultaneous administration of dihydrostreptomycin by the intramuscular route and oxytetracycline or chlortetracycline by the oral or intravenous route. The patient receives 1 gm. of dihydrostreptomycin twice daily. At the same time he receives 750 mg. of oxytetracycline or chlortetracycline by the oral route every 6 hours. If for any reason the patient is unable to tolerate the medication orally, he should be given either of the cyclines by the intravenous route. The usual dose is 500 mg. every 12 hours. The intravenous preparation should be given in 250 cc of solvent over a period of approximately 15 to 20 minutes. The injections should always be made into the veins of the upper extremities. Blood cultures should be obtained every 48 hours, and treatment should be continued until two or three consecutive cultures have been negative and the patient has remained afebrile for at least 48 to 72 hours.

Bacteremia caused by Proteus vulgaris. Bacteremia due to Proteus vulgaris is not as commonly encountered as that due to the coliform organisms. Opinions differ concerning the treatment of choice. I favor the combination of dihydrostreptomycin administered by the intramuscular route simultaneously with oxytetracycline given by either the oral or the intravenous route in the dosage which has already been mentioned. See table 1.

Bacteremia caused by Pseudomonas aeruginosa. Fortunately, bacteremia due to Pseudomonas aeruginosa is not common. Its treatment is difficult. Experience to date clearly indicates that polymyxin B (aerosporin) is the antibiotic of choice

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TABLE 1. *Bacteremia*

Organism	Antibiotic	Daily Dose	Method of Administration
Coliform group	Dihydrostreptomycin Oxytetracycline or chlortetracycline	2 gm. 3 gm.*	I.M. Oral
Pseudomonas aeruginosa	Polymyxin B	100 to 200 mg.	I.M.
	Polymyxin B Oxytetracycline or tetracycline	50 mg. 3 gm.*	I.M. Oral
Proteus vulgaris	Dihydrostreptomycin Oxytetracycline	2 gm. 3 gm.*	I.M. Oral
Streptococcus pyogenes	Penicillin	1 million U.	I.M. or I.V.
Micrococcus pyogenes			
Penicillin-sensitive	Penicillin (aqueous or procaine)	1 to 2 million U.	I.M. or I.V.
Tetracycline-sensitive	Tetracycline, oxytetracycline or chlortetracycline	3 gm.*	Oral
Erythromycin-sensitive	Erythromycin	1.2 gm.‡	Oral

* I.V. *dose 0.5 gm. every 12 hours.*
‡ I.V. dose 200 mg. every 6 or 8 hours.

in the treatment of this infection. The recommended dose is 100 to 200 mg. daily. This amount should be given in isotonic sodium chloride solution by the intramuscular route in divided doses four times daily. In other words, 25 to 50 mg. is administered every 6 hours. Severe pain at the site of injection is a troublesome side reaction. However, the most serious toxic reaction is the occurrence of paresthesia and cerebellar ataxia. For this reason the course of therapy should be of short duration.

The recent studies of Bunn and his associates[1] are welcomed by those interested in the treatment of bacteremia owing to Pseudomonas aeruginosa. These investigators have shown that there is a synergistic effect of polymyxin B and oxytetracycline, as well as tetracycline, upon the growth of Pseudomonas aeruginosa. They report sterilization of the urinary tract with a dose regimen of 25 mg. of polymyxin B given by the intramuscular route once daily, combined with 2 gm. of either oxytetracycline or tetracycline given by the oral route. The reduced dose of polymyxin B required by this regimen makes it possible to treat this infection with amounts of polymyxin well below the neurotoxic level.

Therefore, this combination of antibiotics would appear at the moment to be the method of choice in the treatment of bacteremia due to Pseudomonas aeruginosa which arises as a result of infection in the urinary tract. I would be inclined to recommend the use of 25 mg. of polymyxin B by the intramuscular route twice daily and 3 gm. of oxytetracycline or tetracycline by the oral route daily. See table 1.

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[1] Bunn, Paul, Canarile, Leonard and Osborne, Winifred: Synergistic effect of polymyxin B and oxytetracycline or tetracycline upon growth of Pseudomonas aeruginosa. Read at forty-sixth annual meeting of American Society for Clinical Investigation, Atlantic City, New Jersey, May 3, 1954.

Streptococcic bacteremia. Bacteremia due to Streptococcus pyogenes, as well as bacteremia due to anaerobic or microaerophilic strains of streptococci, presents no great problem to the clinician. The method of choice in the treatment of bacteremia owing to these organisms is the daily administration of 1 million units of penicillin by either the intramuscular or the intravenous route. See table 1. The only indication for the use of the newer antibiotics in the treatment of streptococcic bacteremia is when the patient is known to be allergic to penicillin.

Staphylococcic bacteremia. The successful treatment of bacteremia caused by Micrococcus pyogenes is dependent upon the precise knowledge of the sensitivity of the organism to the available antibiotics. The results of treatment are likely to be disappoining if the clinician does not have available adequate bacteriologic facilities. When penicillin first was available, the management of staphylococcic bacteremia arising from the urinary tract was a simple matter. Nearly 80 per cent of patients with staphylococcic bacteremia responded to the administration of adequate doses of penicillin. The emergence of penicillin-resistant strains of staphylococci led to the use of chlortetracycline and oxytetracycline, which in the beginning also was followed by gratifying results. However, today approximately one-half of the strains of Micrococcus pyogenes isolated are found to be resistant to both of the cyclines. Fortunately, most of the organisms are sensitive to erythromycin, and at the moment this is the antibiotic of choice in the treatment of these patients.

If the organism is found to be sensitive to penicillin, the patient should receive 1 to 2 million units of procaine penicillin by the intramuscular route or 1 to 2 million units of aqueous penicillin by the intravenous drip method daily. If the organism is found to be resistant to penicillin but sensitive to one of the cyclines, the patient should receive 750 mg. of either oxytetracycline or chlortetracycline every 6 hours by the oral route. If the patient is unable to tolerate the cyclines by mouth, he should receive 0.5 gm. by the intravenous route every 12 hours. If the organism is resistant to both penicillin and the cyclines but sensitive to erythromycin, the patient should receive the latter antibiotic in full therapeutic doses. The recommended dose of erythromycin is 300 mg. by the oral route every 6 hours. The recommended dose of erythromycin for intravenous administration is 200 mg. every 8 hours. At times it may be desirable to combine full therapeutic doses of erythromycin and full therapeutic doses of penicillin in the treatment of these patients. However, it is not recommended that either penicillin or erythromycin be combined with any of the cyclines. See table 1.

In the treatment of staphylococcic bacteremia it is exceedingly important to continue therapy until three or more successive blood cultures have been negative and the patient has remained afebrile for 72 to 96 hours.

BACTERIAL ENDOCARDITIS

Experience clearly indicates that there are three types of endocarditis which may arise as a result of infection of the urinary tract: endocarditis due to invasion of the heart valve by Neisseria gonorrhoeae, endocarditis due to Micrococcus pyogenes, and endocarditis (subacute) due to invasion of a previously damaged heart valve by Streptococcus faecalis. These three types of endocarditis are of considerable interest to the urologist, and the management of each type will be discussed separately.

Endocarditis due to Neisseria gonorrhoeae.—At the present time this type of endocarditis is rare. Early treatment of Neisserian infections using adequate doses of penicillin or any of the other effective antibiotics has virtually eliminated this disease. It is highly probable that its occurrence will be relegated to the annals of medical history.

Staphylococcic endocarditis.—Staphylococcic endocarditis, to the urologist and his medical colleagues, is an extremely difficult and perplexing disease. Although its occurrence is not common, when it does occur, it is difficult to manage and its occurrence is of grave prognostic significance. It usually is the end result of staphylococcic bacteremia which on occasion follows transurethral surgery in a patient who harbors the organism, Micrococcus pyogenes in his urinary tract.

I know of no other instance in which the success of antibiotic therapy is more dependent on the results of sensitivity tests than in this disease. Once the diagnosis has been established, the only possible chance of recovery depends upon intensive treatment using enormous doses of the antibiotic to which the organism has been found to be susceptible. If, by chance, the organism is sensitive to penicillin, I would recommend that at least 10 million units of aqueous penicillin be administered daily by the continuous intravenous drip method. See table 2. If the organism is penicillin-resistant, yet sensitive to one of the cyclines, then one of the latter antibiotics should be given in amounts of either 3 gm. per day by the oral route or 1 gm. per day by the intravenous route. If, by chance, the organism is sensitive only to erythromycin (as is likely to be the case at the present time), then this antibiotic is the one of choice. If the patient is able to take erythromycin by the oral route, the recommended initial dose is 400 mg., followed every 6 hours by 300 mg., and this dose should be continued until recovery occurs. The recommended intravenous dose is 200 mg. every 6 or 8 hours.

Streptococcus faecalis endocarditis.—Unlike staphylococcic endocarditis, this is a true example of subacute bacterial endocarditis, which occurs as a result of invasion of a previously damaged heart valve by the organism, Streptococcus faecalis. Its successful treatment is quite different from the management of subacute bacterial endocarditis due to Streptococcus salivarius or Streptococcus mitis. It is a well established fact that the simultaneous administration of 1 to 2 million units of penicillin and 2 gm. of dihydrostreptomycin per day for 2 weeks usually will be successful in the treatment of subacute bacterial endocarditis due to either Streptococcus salivarius or Streptococcus mitis.

The successful treatment of subacute bacterial endocarditis due to Streptococcus faecalis is an entirely different matter. Subacute bacterial endocarditis due to Streptococcus faecalis is of considerable importance to the urologist, since most of the cases of subacute bacterial endocarditis due to this organism arise as a result of or follow surgical procedures on the urinary tract in patients who had valvular lesions of the heart at the time they were subjected to the urologic procedure.

The treatment of this disease may be divided into two parts: 1) therapy and 2)

TABLE 2. *Bacterial endocarditis*

Organism	Antibiotic	Daily Dose	Method of Administration
Neisseria gonorrhoeae	Penicillin	1 million U.	I.M. or I.V.
Micrococcus pyogenes			
Penicillin-sensitive	Penicillin	10 million U. (minimal)	I.V.
Tetracycline-sensitive	Tetracycline	3 gm.	Oral
		1 gm.	I.V.
Erythromycin-sensitive	Erythromycin	1.2 gm.	Oral
		0.6 gm.	I.V.
Streptococcus faecalis	Penicillin	5 to 10 million U.	I.V.
	Dihydrostreptomycin	2 gm.*	I.M.

* After 14th day reduce dose to 1 gm. daily.

prophylaxis. Once the diagnosis has been established, the following method of treatment is recommended. The patient should receive 5 to 10 million units of penicillin per day, given by either the continuous intravenous drip or the intramuscular method. This should be continued for at least 4 to 6 weeks. During the first 2 weeks of therapy the patient should receive 1 gm. of dihydrostreptomycin by the intramuscular route twice daily. After 2 weeks the dose of streptomycin should be reduced to 0.5 gm. twice daily and continued for the stated period of 4 to 6 weeks, during which time the patient is receiving intensive penicillin therapy. See table 2. It is further recommended that the patient receive small doses of penicillin for a number of weeks and even months after the course of combined penicillin and streptomycin therapy has been completed.

For the administration of the large doses of penicillin which are usually required in the treatment of this infection I prefer the continuous intravenous drip method. This method is best tolerated if the veins of the dorsal surface of the hand or arm are used. Continued use of the veins of the lower extremities may invite venous thrombosis with its complications. I have never seen embolic phenomena or other serious difficulty from venous irritation in the upper extremities. Polyethylene tubes placed in the veins have been extremely helpful in maintaining the continuous intravenous drip. Patients may receive penicillin through the same polyethylene tube for as long as two or more weeks. Thus the entire course of treatment may be completed without changing the intravenous needle more than two or three times.

Heparin is not recommended in the treatment of bacterial endocarditis, but small amounts may be used to aid in the prevention of venous thrombosis at the site of injection. For this purpose 25 mg. of heparin sodium is added to each liter of solution employed. The daily dose of penicillin usually is administered in 2 liters of solvent. One-half of the daily dose may be given in isotonic sodium chloride solution and the other half in glucose solution. The approximate rate of the drip is 20 drops per minute.

The use of so-called blocking agents to enhance the effect of antibiotics is of some importance in the management of subacute bacterial endocarditis, but in my opinion the use of carinamide or probenecid (benemid) has not often been essential to successful therapy. If blocking agents are to be used, probenecid undoubtedly is the one of choice at the present time. The recommended dose is 0.5 gm. administered four times daily by the oral route. Fortunately, probenecid does not inhibit excretion of streptomycin and therefore can be administered with the penicillin-streptomycin combined therapy method without fear of accumulating toxic values of streptomycin in the blood, while at the same time increasing the serum levels of penicillin.

If suitable antibiotic therapy is employed and if the dose and duration of treatment are adequate, from 60 to 70 per cent of patients with subacute bacterial endocarditis should recover. When recovery occurs, the physician should remember, however, that these patients have damaged heart valves. Their activity should be limited to some degree, commensurate with the extent of irreversible cardiac damage that has occurred.

I know of no situation in which the prophylactic use of antibiotics is more justified than in the prevention of subacute bacterial endocarditis due to Streptococcus faecalis following transurethral or other manipulative procedures in the urinary tract. This does not imply that antibiotics should be administered routinely to every patient who is to undergo a urosurgical procedure. However, it does imply that no patient should be subjected to transurethral or other operative procedures until he has undergone a careful physical examination to determine the presence or absence of valvular lesions of the heart. If a heart murmur exists, the patient should receive 1 million units of penicillin and 1 gm. of dihydrostreptomycin the day of and for several days following the surgical procedure. It is my conviction that this regimen will to a large degree prevent the development of subacute bacterial endocarditis due to Streptococcus faecalis in patients who have organic heart murmurs and who must undergo urosurgical procedures.

LOCALIZED INFECTIONS

Let us now consider the management of those infections of the urinary tract which may occur as a result of primary systemic infections. There are a number of infections of the urinary tract which occur as a part of an acute systemic infection and which are transient. These do not concern us at the moment. By a localized infection is meant an infection of the urinary tract which is more or less chronic and which localizes and remains in the urinary tract after the primary systemic infection has subsided. The two most important infections of this type are tuberculosis and brucellosis.

Tuberculosis. The advances in chemotherapy have considerably altered the management, as well as the prognosis, of renal and genito-urinary tuberculosis. It was clearly evident that streptomycin was definitely suppressive. However, the introduction of combined therapy has improved the results in the treatment of this disease. It would appear that the method of choice in the treatment of tuberculosis in the urinary tract at the present time is a combination of streptomycin and isoniazid, or a combination of streptomycin and para-aminosalicylic acid, or a combination of all three of these agents used simultaneously. Combined therapy delays the emergence of resistant strains of Mycobacterium tuberculosis.

For the first few days of treatment it has been my practice to administer strep-

TABLE 3. *Localized infections*

Organism	Therapeutic Agent	Daily Dose	Method of Administration
Mycobacterium tuberculosis	Dihydrostreptomycin	1 gm.*	I.M.
	Isoniazid	150 to 200 mg.	Oral
	Para-aminosalicylic acid	12 to 16 gm.	Oral
	Pyrazinamide		
	Isoniazid	150 to 200 mg.	Oral
Brucella abortus suis melitensis	Dihydrostreptomycin	2 gm.‡	I.M.
	Oxytetracycline or chlortetracycline	3 gm.	Oral

* Either biweekly or triweekly.
‡ After 14th day reduce dose to 1 gm. daily.

tomycin in amounts of 1 gm. daily by the intramuscular route. After this the patient receives 1 gm. of dihydrostreptomycin sulfate 3 days per week. At the same time he receives from 150 to 200 mg. of isoniazid daily by the oral route. If streptomycin and isoniazid are combined with para-aminosalicylic acid, the patient receives the latter drug in amounts of 3 to 4 gm. three or four times daily by the oral route. See table 3. Most investigators agree that treatment should be continued for 12 to 18 months.

The recent report of McDermott and his colleagues[2] on the influence of pyrazinamide combined with isoniazid in the treatment of infections owing to Mycobacterium tuberculosis in animals and man is indeed interesting. It would appear from their studies that this combination of chemotherapeutic agents more nearly approaches complete inhibition than any previously reported method. In spite of lack of evident toxicity in animals, they report some hepatotoxicity in humans using this combination. However, in certain desperate circumstances one might consider the use of this method in those cases which were refractory to other accepted forms of treatment.

Brucellosis. It is my conviction that localized brucellosis of the urinary tract is more common than is generally recognized. There are several reasons why the infection may not be recognized. First is the lack of suspicion on the part of the clinician of the possibility that the disease may exist. Second is the fact that, unless special techniques are employed for the bacteriologic study of the urine, the disease cannot be identified. Furthermore, chronic brucellosis of the urinary tract may closely mimic tuberculosis. If the clinical picture in the urinary tract suggests tuberculosis but the organism Mycobacterium tuberculosis cannot be identified, special bacteriologic studies for Brucella should be carried out. The routine methods of culture used for the identification of pyogenic organisms will not identify Brucella in the urine or tissues. The method of choice for culturing specimens for Brucella is the method of Castaneda or a modification of this method. Renal brucellosis is an example of localized brucellosis. There is usually present a history of previous undulant fever, although the primary infection may not have been recognized. Agglutinations for Brucella are helpful but not entirely diagnostic. Furthermore, the agglutination titers probably will be in low dilutions; in fact, they may even be negative. It should be emphasized further that Brucella abortus, Brucella suis, or Brucella melitensis can be isolated from the urine of patients suffering with this disease. Once the diagnosis has been established, treatment is available.

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[2] McDermott, Walsh, Tompsett, Ralph, McCune, Robert, Ormond, Louise, Deuschle, Kurt and Muschenheim, Carl: The influence of pyrazinamide-isoniazid on M. tuberculosis in animals and man. Read at sixty-seventh annual meeting of Association of American Physicians, Atlantic City, New Jersey, May 4, 1954.

In the past, various forms of treatment have been employed in the management of brucellosis. Sulfonamides were found to be suppressive. Likewise, streptomycin had some suppressive effect on the course of the disease. Some improvement in results occurred using combinations of streptomycin and sulfonamides. Some investigators have been enthusiastic about the value of chloramphenicol or aureomycin or terramycin used alone in the treatment of this infection. The clinical and bacteriologic relapse rates following any of these forms of treatment have been high.

To date the most effective method for the treatment of either acute or localized brucellosis is the combination of dihydrostreptomycin and either chlortetracycline or oxytetracycline, as has been previously reported by Barber and me.[3] It should be emphasized that this method of treatment involves the simultaneous use of the two antibiotics and not a course of terramycin or aureomycin followed by a course of dihydrostreptomycin. The following plan of treatment is recommended for localized brucellosis of the urinary tract. The patient receives 1 gm. of dihydrostreptomycin sulfate morning and evening for 12 to 14 days. At that time the dose is reduced to 0.5 gm. twice daily and continued for 4 to 6 weeks. Simultaneously the patient receives by the oral route 750 mg. of either chlortetracycline or oxytetracycline every 6 hours. See table 3. This is continued for the same period of time that the patient receives streptomycin.

The reason for reducing the dose of streptomycin at the end of 2 weeks is simply a matter of avoiding neurotoxicity. If there is no impairment of renal function, there is no danger of toxicity from the doses recommended. If there is impairment of renal function, then the dose of streptomycin is reduced to one-half. To follow the response to treatment it is recommended that biweekly cultures of the urine for Brucella be made.

SUMMARY

The successful treatment of infections of the blood stream and heart which result from infections originating in the urinary tract is dependent upon 1) early recognition of the disease, 2) precise knowledge of the sensitivity of the organism to the chemotherapeutic agent, and 3) adequate treatment continued over a sufficient period of time to eliminate the organism from the blood stream. Likewise, the removal of foci is equally important. Bacteremia due to organisms of the coliform group responds best to treatment with combined therapy consisting of the simultaneous use of dihydrostreptomycin and one of the tetracyclines. A combination of streptomycin and tetracycline may prove to be equally effective. Bacteremia caused by Pseudomonas aeruginosa should be treated with polymyxin B (aerosporin) or a combination consisting of the simultaneous administration of small doses of polymyxin B and full therapeutic doses of either oxytetracycline or tetracycline given by the oral or intravenous route. Bacteremia due to Streptococcus pyogenes can be effectively treated using full doses of penicillin given by either the intramuscular or intravenous method. Staphylococcal bacteremia due to penicillin-resistant strains of Micrococcus pyogenes will respond to intensive therapy with tetracycline, oxytetracycline or chlortetracycline. In those instances where the organism is penicillin- and tetracycline-resistant, the method of choice at the present time is intensive treatment with either oral or intraveous erythromycin.

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[3] Herrell, W. E. and Barber, T. E.: Treatment of brucellosis with aureomycin or terramycin combined with dihydrostreptomycin. Postgrad. Med., 11: 476–486, 1952.

Endocarditis which arises as a result of primary infection in the urinary tract requires much more intensive and prolonged treatment than bacteremia. Methods for treating these infections have been outlined. No patient with demonstrable evidence of valvular heart disease should undergo a urosurgical procedure without the benefit of prophylactic antibiotic therapy.

The two most important types of localizing infection of the urinary tract consist of tuberculosis and brucellosis. The method of choice in the treatment of infections of the urinary tract due to Mycobacterium tuberculosis consists of the prolonged use of combined therapy which employs streptomycin and isoniazid, or streptomycin, isoniazid and para-aminosalicylic acid. Under certain conditions the use of a combination of pyrazinamide and isoniazid may be justified.

Brucellosis of the urinary tract is often unrecognized, but methods for its diagnosis and treatment are available. The most effective method of treatment for brucellosis of the urinary tract consists of the simultaneous administration of streptomycin with oxytetracycline or the simultaneous administration of streptomycin with chlortetracycline. Treatment should be intensive and prolonged.

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URINARY TRACT INFECTIONS: EXPERIENCE WITH ELKOSIN*

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This paper is presented to 1) review the pertinent facts relating to urinary tract infection, 2) to report on the use of elkosin during the past year in the Department of Urology at Veterans Administration Hospital, Hines, Illinois, and 3) to report the results obtained in 23 cases of uncomplicated urinary tract infections treated with elkosin.

Urinary tract infections are a basic problem in Urology and frequently confront almost every practicioner of medicine. Few urological problems can be solved expeditiously without recognition and proper treatment of any existing urinary tract infection. Fully 75 per cent of urological cases are complicated by infection in the urinary tract during the course of treatment.

PRINCIPLES OF DIAGNOSIS

Symptoms alone are not sufficient to make a diagnosis of urinary tract infection; the presence of bacteria or leukocytes in the urine is necessary to establish the diagnosis. Symptoms in the female may be due to nonpurulent chronic urethritis, or in the male to nonspecific prostatitis or posterior urethritis.

In acute infections, identification of the organism should be accomplished.

In chronic or recurring infections, the urinary tract must be investigated when the history or physical examination suggests complicating pathological changes such as involvement of the upper urinary tract, calculi, pyelonephritis, flank masses, urinary obstruction, congenital anomalies, or prostatic enlargement. A work-up of the patient should include excretory urography, cystoscopy when the acute infection has subsided, evaluation of renal function, and retrograde pyelography, if indicated.

Patients with severe infections should be hospitalized for diagnosis and treatment when there is marked pyrexia, pain, dehydration, vomiting, and need for supportive therapy.

METHODS OF DIAGNOSIS

Urinalysis. Careful examination of the urine will give valuable information in the diagnosis and treatment of urinary tract infections. Urine should be examined for color, pH, albumin, sugar, and for microscopic elements.

Cloudy urine does not always indicate infection, since crystals in the urine may produce cloudiness. Most commonly, these crystals are phosphates, oxalates, and carbonates, and are found in alkaline urine. Acidification of the urine with 5 per cent acetic acid will usually cause the crystals to dissolve.

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[illegible] 30, 1954.

[illegible] ,6 Dimethyl-4-pyrimidyl)-sulfanilamide. The drug used in [illegible] a Pharmaceutical Products.

Certain organisms, notably of the Proteus group, will split urea molecules, giving ammonia and an alkaline urine. The presence of an alkaline urine with many pus cells should lead one to suspect a urea-splitting organism, and this is most commonly Proteus vulgaris.

Albumin is present in many urinary tract infections due to tissue breakdown and pus cells. If albumin is present and no pus cells are found, the possibility of organic or parenchymal kidney disease should be investigated.

The presence of sugar and the absence of pyogenic organisms in the urine should lead one to think of a Monilia infection, particularly in women who complain of pruritis.

The finding of bacteria or pus cells microscopically in the urine justifies the diagnosis of urinary tract infection, although the presence of one or two white cells or an occasional red cell in the uncentrifuged urine may be considered normal. Over one or two white cells in the uncentrifuged or over eight or ten white cells per high power field from the centrifuged specimen should be considered pathological. Bacteria are best observed for shape with a gram stain.

Gram stain. When culture is not available, a Gram stain made from the urine dried on a slide over a flame is recommended by some to classify the organisms for therapeutic purposes. Shaw has grouped the organisms in categories distinguishable by the Gram stain on the justification that organisms in each group are generally sensitive to the same antibiotics. The four groups are: Gram negative bacilli, streptococci, staphylococci, and streptococcus faecalis.

Culture. The only method for determining the etiological organism in urinary tract infection is a urine culture. This should be taken on the first office visit before the patient is given any antibiotic therapy.

Proper collection of the urine for culture is essential to avoid contamination. Prompt inoculation of bacteriological plates should be done; if this is not possible, the urine should be refrigerated.

In the male patient, a voided specimen is satisfactory for culture. The foreskin should be retracted and the meatus cleansed thoroughly with alcohol or green soap and water. Approximately 100 cc of urine should be discarded, following which a specimen of 50 to 100 cc should be collected in a sterile bottle. The culture bottle should be covered with a sterile cover and labeled accurately with the name and date.

The female patient should be draped lying with the knees elevated and apart. Under good light, the urethral meatus should be cleaned thoroughly of vaginal secretion with tincture of green soap and water. A sterile catheter should be passed and the first few cubic centimeters of urine discarded. Urine should be collected in a sterile bottle with a sterile cover and accurately labeled with name and date.

Sensitivity studies. Recently small discs of most antibiotics have become available with which the relative sensitivity of an organism to a given antibiotic can be determined. This enables the physician to select the antibiotic to which the organism is most sensitive.

In general, organisms of a group will be most sensitive to one antibiotic.

Following treatment, an organism frequently develops a resistance to the antibiotic used as may be demonstrated by repetition of the sensitivity tests.

Sensitivity studies with the sulfas are inaccurate. Individual variation in the percentage of acetylation and rate of excretion distort *in vivo* and *in vitro* correlation.

BACTERIOLOGY

Many large series of cultures have been reported in the literature and the colon bacilli are always the most common offenders. Herrold reports the colon bacilli to be the causative organisms in 90 per cent of urinary tract infections. Flint reports E. coli recovered in 41 per cent of his cases. The organisms commonly cultured from the urinary tract are listed in the table below and are classified according to their gram stain.

Gram Negative

Escherichia coli
Aerobacter aerogenes
Proteus vulgaris
Pseudomonas aeruginosa (Bacillus pyocyaneus)
Alcaligenes faecalis
Paracolon bacillus

Gram Positive

Streptococcus faecalis
Streptococcus (hemolytic and nonhemolytic, alpha, beta, and gamma)
Staphlococcus (albus and aureus)

These are listed in approximate order of frequency of recovery, except that Streptococcus faecalis should be near the top.

Fortunately, the most common offender, E. coli, is one of the most responsive to therapy. The Proteus and Pseudomonas groups of organisms are the most difficult to eradicate from the urinary tract.

PRINCIPLES OF THERAPY

There are two basic principles necessary for proper treatment of any urinary tract infection. First, the organism must be identified and treated with an appropriate antibiotic to which the patient is not allergic. Second, any underlying pathological processes in the urinary tract producing obstruction and stasis of urine must be eliminated before permanent cure can be obtained.

On the first visit, a culture of the urine should be obtained and the patient placed on a relatively innocuous, inexpensive, and wide range antibiotic such as one of the sulfas. The sulfas are effective against most of the common urinary tract organisms.

If the organism is not sensitive to sulfa, the antibiotic should be changed to an appropriate one. Selection of the proper drug should be based on identification and sensitivity of the organism. If sensitivity tests are not available, the best drug for the organism cultured should be selected according to table 1, which summarizes the drug of choice from the medical literature on the subject.

Treatment should continue for a minimum of seven to ten days, and longer

TABLE 1. *Common urinary tract organisms and drugs of choice for each*

Organism	Drugs of Choice Listed as First (1), Second (2), and Third (3) Choice
Escherichia coli	1. Elkosin or gantrisin 2. Aureomycin, terramycin, chloromycetin 3. Mandelamine
Aerobacter aerogenes	1. Aureomycin, terramycin, or chloromycetin
Proteus vulgaris	1. Furadantin* 2. Chloromycetin, elkosin or gantrisin
Pseudomonas aeruginosa	1. Terramycin 2. Streptomycin or polymixin*
Alcaligenes faecalis	1. Terramycin, aureomycin
Paracolon bacillus	1. Aureomycin, terramycin
Streptococcus faecalis	1. Mandelamine 2. Terramycin, aureomycin
Streptococcus	1. Penicillin plus elkosin or gantrisin 2. Aureomycin, terramycin, erythromycin in penicillin resistant cases
Staphylococcus	1. Penicillin plus elkosin or gantrisin 2. Aureomycin, erythromycin in penicillin resistant cases

* Relatively new, but shows some promise; observe precautions for toxicity.

for the more resistant organisms. If the infection recurs or persists, the patient must be investigated to determine the cause of recurrence or chronicity.

Diabetes, if present, must be brought under control. Fluids should be given freely in cases with good kidney function. Alkalinization or acidification is not of proven value except for Proteus infections, in which an attempt should be made to acidify the urine. Orally administered agents such as pyridium and serenium which are excreted in the urine and produce topical anesthesia may give the patient prompt relief from urgency and frequency.

Therapeutic failures are relatively common and justify further investigation. Failure to remedy the underlying process can lead only to recurrent infection. Nesbit states that stasis of urine is the most common obstacle to the cure of urinary tract infection. Other causes for failure are malignant disease, the presence of calculi, repeated instrumentation, the use of indwelling drainage tubes, the presence of tuberculosis, inadequate dosage of the antibacterial agent, or a resistance of the organism to the antibiotic used.

Many cases clear rapidly but relapse despite a continuance of the therapy when an organism grows which previously was not present. These organisms which develop are usually ones which are not sensitive to the antibacterial agent being used. In such cases another agent should be chosen.

Some urologists prefer to administer combinations of drugs simultaneously. Others prefer to use one drug at a time to maintain a reserve of anti-bacterial agents for use if resistance in the organism or allergy in the patient develops.

ELKOSIN

This study was undertaken to further evaluate the antibacterial activity of elkosin in the therapeutic and prophylactic treatment of urinary tract infections, and to note the presence of any untoward reactions.

Elkosin possesses attributes which are desirable for antibiotics used in the treatment of urinary tract infections: ease of administration, low cost, high percentage of excretion in the urine, high solubility, low acetylation, and low toxicity.

Elkosin is a sulfanilamide derivative which is exceptionally soluble. It has a solubility in urine in the free state of 362 mg. per cent at pH 5.5 and 600 mg. per cent at pH 6.5. This is more soluble than gantrisin which will dissolve 60 mg. per cent at pH 5.4 and 327 mg. per cent at pH 6.14. Both elkosin and gantrisin are considerably more soluble than sulfadiazine, sulfamerazine, and sulfathiazole. Sulfadiazine has a solubility of only 12.9 mg. per cent at pH 6.2; its solubility rises rapidly to levels comparable to gantrisin and elkosin only at about pH 7.5. The acetylated form is less soluble than the free for both elkosin and gantrisin, whereas with sulfadizine, the reverse is true.

The high solubility of elkosin makes the possibility of crystallization in the kidney highly improbable even with a decreased urinary output.

All of the sulfa drugs are acetylated to some degree by the body and are excreted in the urine in the free and acetylated forms. The acetylated form has little or no antibacterial activity.

Previous studies have shown elkosin is excreted in the urine an average of 87 per cent in the free form and 13 per cent in the acetylated form. Gantrisin is excreted an average of 70 per cent in the free form and 30 per cent in the acetylated form. Sulfadiazine is acetylated in a greater percentage than either elkosin or gantrisin.

Elkosin and gantrisin have approximately equally rapid rates of absorption from the intestinal tract, equal blood levels, and approximately equal (90 per cent) excretion in the urine after 48 hours.

Toxic and untoward reactions are very few. One fatal case of agranulocytosis has been reported by Iacobaeus.

Elkosin has been used in Europe for over 10 years. Iacobaeus and Gsell have reported favorable results with elkosin in the treatment of infections. Commons and Wire reported the results of 56 patients treated with elkosin in which the elkosin was found to be a safe and effective antibacterial agent in urinary tract infections. Herrold suggests the use of elkosin or gantrisin where sulfonamide derivatives are indicated in urinary tract infections.

EXPERIENCE WITH ELKOSIN

Elkosin has been used extensively for one year in the Department of Urology at Hines. Many patients with indwelling drainage systems and those receiving repeated instrumentation have received elkosin prophylactically. Patients have been treated preoperatively by elkosin. Postoperatively, elkosin has been combined with penicillin, aureomycin, terramycin, or chloromycetin. One case of transurethral resection was treated by elkosin alone (with near disaster). Urinary tract infections, simple and complicated by obstruction, have been treated with elkosin. When organisms did not or could not be expected to respond to sulfa therapy, an additional antibiotic was used.

All patients were treated with one gram of elkosin given orally four times a day. No parenteral elkosin was used, although elkosin is reported to be well tolerated intramuscularly or intravenously.

An estimated 300 or more patients have been treated with elkosin. The results of prophylactic use were considered satisfactory except for two failures.

In the one patient treated with elkosin alone following a transurethral resection severe periprostatitis and bilateral pyelonephritis developed. Urine culture showed Proteus vulgaris.

Another patient, on elkosin prophylactically, with an indwelling catheter for strictures also had a severe urinary tract infection from which Proteus vulgaris was cultured.

From the many urinary tract infections treated with elkosin, all cases without evidence of obstruction were selected for detailed study. There were 23 cases in this category.

One week was considered a course of treatment. The patient was evaluated as to symptoms, the urine examined microscopically, and recultured at the end of each course of treatment. If the urine was not sterile at the end of three weeks, the treatment was discontinued and declared a bacteriological failure.

The organisms cultured, their frequency of occurrence, alone and with other organisms, and the results of therapy are presented in table 2.

Subjectively, 21 patients were relieved or had less symptoms whereas two were unimproved. One of these was due to B. proteus, and the other to Streptococcus faecalis.

The results with E. coli were constantly good and all eight cases promptly became bacteriologically negative.

TABLE 2. *Results in 23 cases of urinary tract infection treated with elkosin*

Organism	Occurrence		Clinical Evaluation		Bacteriological Evaluation		
	Alone	With other organism	Improved	Unimproved	Urine sterile	Failure	Occurrence following therapy for another organism
Escherichia coli	5	3	8		8	0	0
Strep. faecalis	5	1	5	1	4	2	5
Pseudomonas	1	3	4		3	1	1
B. proteus	2	2	3	1	3	1	1
Alcaligenes faecalis	0	3	3		2	1	3
Aerobacter aerogenes	2	0	2		1	1	0
Staphylococcus	1				1	0	0
Streptococcus	1				1	0	0

Of six cases in which Streptococcus faecalis was cultured originally, four became bacteriologically negative. However, Streptococcus faecalis was cultured five times in other cases following one or more weeks of elkosin therapy. These latter cases should be considered as failures of elkosin to control this organism.

Three out of four urinary tracts from which B. proteus and Pseudomonas organisms were cultured were rendered sterile. Each of these organisms, however, was cultured following a course of therapy for a different organism.

Alcaligenes faecalis was found four times after elkosin therapy, once as a persistent culture and three times as an organism not present at the start of therapy. Two Alcaligenes cultures were rendered sterile.

Of two cases with Aerobacter aerogenes, both were improved clinically and one culture became negative.

One culture each of staphylococcus and streptococcus was rendered sterile following elkosin therapy. Single cases are an inadequate basis for a conclusion.

For the first three months of the study, blood counts were made weekly on all patients treated with elkosin. No cases of leukopenia or agranulocytosis were noted.

No patients had nausea, vomiting, diarrhea or skin rashes.

Two patients with indwelling ureteral catheters and treated with elkosin for several months had fever without evidence of infection. Fever disappeared in each following discontinuation of the drug.

The urines of 23 patients studied for urinary tract infection were carefully examined for sulfa crystals and none were found.

CONCLUSIONS

Twenty-one of twenty-three patients with urinary tract infection treated with elkosin were clinically improved.

Elkosin was 100 per cent effective in eliminating E. coli organisms from the urinary tract of individuals with uncomplicated urinary tract infection.

Elkosin is considered ineffective in infections of the urinary tract due to Streptococcus faecalis.

Elkosin has proved a safe drug and has a very low incidence of untoward reactions.

SUMMARY

The basic facts and concepts pertaining to urinary tract infections have been discussed. A brief review has been made of the experience with elkosin during the past year, and the results obtained in 23 cases of uncomplicated urinary tract infections have been presented.

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A TECHNIQUE FOR RETRORECTAL GAS INSUFFLATION

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The roentgen demonstration of retroperitoneal masses and structures has long been known to be facilitated by the introduction of gas into the retroperitoneal areolar tissue. This was first discovered accidentally by Carelli in 1921, when he found that carbon dioxide introduced into the renal fascia outlined the kidney, kidney capsule, and adrenal. Carelli and his co-worker, Sordelli, conceived of the technique of retroperitoneal gas insufflation when they discovered a perirenal emphysema, with good visualization of the kidneys, in a patient on whom they were performing a pneumoperitoneum. Their original technique was dangerous and eventually was practiced only in exceptional cases because of the risks involved. As originally performed clinically, the procedure consisted in the injection of gas, by a variety of means, into the perirenal tissue beneath Gerota's fascia through a long lumbar needle. This technique was called retro-pneumoperitoneum by European investigators, but the term extraperitoneal pneumography appears to be preferable since it indicates a diagnostic procedure, and organs such as the liver and spleen, which are not retroperitoneal, may be examined by this means.

By and large the procedure was followed by satisfactory roentgen results. Numerous drawbacks were quickly noted, however, some in the nature of inconvenience, others in the realm of the frankly dangerous. First of all, a high degree of technique was necessary with regard to proper placement of the needle. Gas injected too deeply occasionally resulted in a pneumopyelogram, an interesting but infrequently rewarding study. Gas injected too superficially merely dissected the parietal fascia or muscular layers of the body. Serious complications were almost always the consequence of intravascular injection of gas, with fatal air embolism being not infrequently reported. Aspirating the needle prior to injection cannot guarantee safety against this complication as thin-walled veins collapse when suction is applied and blood fails to appear in the aspirating syringe, even though the needle tip lies within the vessel, and, of course, will inject satisfactorily. There are reports of accidents due to injection of gas into the renal vein and artery or their tributaries, the aorta and the inferior vena cava, the intestine, particularly the duodenum and splenic flexure, and the cisterna chyli. With the employment of reasonable asepsis retroperitoneal infections have not constituted a significant hazard. Accurate positioning of the needle becomes increasingly difficult with obesity, a particularly important disadvantage since a large proportion of patients who are candidates for the procedure are obese endocrine problems.

Evidencing the difficulties and hazards imposed by this technique, which was popularized in this country by Cahill in 1935, are the remarks of Barquín. This author reported in 1947, that he always does perirenal air insufflations in the operating room and never in the x-ray department or office. His reasons for this

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are as follows: The position that is required is not easily obtained except on the operating table with a Pillet support. In addition, he desired to have oxygen, the resuscitating machine, and central and peripheral stimulants available in the event of accident. He further feels that the procedure must be carried out under aseptic conditions of a degree which cannot be secured outside of the operating room.

As utilized by Cahill, who reported a modification of the original technique, air was injected by means of a hand syringe directly into the perirenal space. Once injected the air was manipulated by hand. He found that slow fascial plane infiltration would take place and x-rays taken 12, 18, 24, or 36 hours later would bring out the organs and fascial planes very clearly, especially around the adrenals. No ill effects were reported from the procedure using 200–250 cc of air depending on the size of the patient. Mencher increased the volume of gas used to 550 cc for a unilateral examination but felt the danger of gas embolus to be sufficiently great to warrant the slower injection of gas by the use of a gravity drip gas displacement method.

The development of the retrorectal, presacral, or paracoccygeal site for gas insufflation by Ruiz Rivas in 1950, has eliminated many of the undesirable features of perirenal insufflation. The ease and safety of utilizing this route for gas introduction into the retroperitoneal tissues to produce a diffuse and extensive emphysema have been amply demonstrated by its application in several thousand cases with an extremely low incidence of accidents and failures. Coupled with the simultaneous use of intravenous or retrograde pyelography and laminography, this procedure has provided spatial localization of retroperitoneal masses heretofore not obtainable. The organs which may be studied by this technique may include the uterus, adnexa, kidneys, bladder, adrenals, liver and spleen. The structures of the mediastinum and neck may be outlined if large quantities of gas are used. In the urological field, failure of gas to dissect around a kidney has been found to be a sign of extrarenal extension of a malignant neoplasm or of perinephritis. Unsuspected nonfunctioning halves of double kidneys have been demonstrated by retroperitoneal air contrast. Peripheral renal masses which fail to deform the collecting system as visualized in pyelograms and which produce no discernible bulge on the convex renal surface on conventional films have been identified by this method. Lateralization of suspected adrenal tumors has been accomplished with a single examination. Diagnostic statements concerning adrenal hypertrophy, hyperplasia, or atrophy cannot be made on the basis of this method in our hands.

We have devised a simple modification of the technique of retrorectal insufflation which has resulted in marked increase in ease of performance, shortening of the time required for injection, and increased comfort for both the patient and the operator.

METHOD

We have utilized a hand syringe for the introduction of the gas in more than 100 cases without noting any embolic phenomena or other accidents. No attention is given to the pressure used. Cahill, performing perirenal insufflation, reported no accidents utilizing a hand syringe in a similar fashion. The avascularity of the region as well as allowing some time to elapse between the placement of the needle and beginning injection has doubtless contributed to the absence of accidents. Oxygen is used as the medium for contrast. Its absorption rate lies between that of carbon dioxide and air and permits time for diffusion through the extraperitoneal tissues. It has a relatively limited tendency to cause serious embolism should a vascular channel be entered.

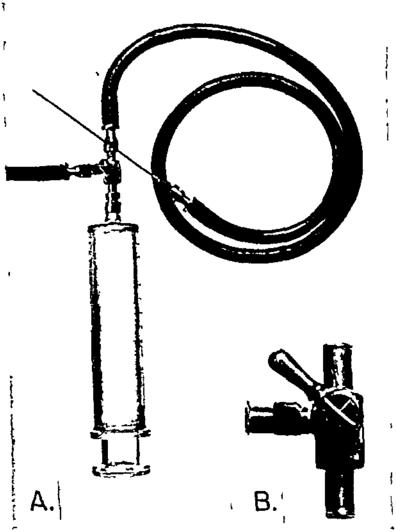

Fig. 1. *A*, injection unit completely assembled. *B*, detail of stopcock. Three female limbs to accommodate pressure lock connections.

After suitable skin preparation of the peri-anal area, the administration of a cleansing enema or suitable cathartic, and a mild sedative, the patient is placed in the knee-chest position in bed or on an examining or x-ray table. The peri-anal skin and sacrococcygeal area are painted with an antiseptic solution and draped with sterile towels. The index finger of one hand is gently inserted into the rectum and the position of the coccyx accurately determined. Immediately lateral to the inferiormost coccygeal segment a skin wheal is raised with procaine and local anesthesia is then carried deeply in front of the coccyx. Palpation with the rectal finger guides the positioning of the infiltrating needle at all times. When anesthesia has been accomplished (usually not more than 5 cc will be required) the infiltrating needle is withdrawn. For the injection of the gas an 18 or 20 gauge three inch standard, short bevel, spinal needle, fitted with an obturator, is used. This is introduced along the anesthetized tract until the tip is felt through the rectal wall. To conform to the inclination of the rectum and sacrum the hub of the needle is depressed and the tip is advanced under constant digital guidance until it comes to lie in the midline opposite the lower segments of the sacrum. It will seldom be necessary to advance the needle more then two inches from the skin to accomplish this. The obturator is removed and the conventional tests are made to ascertain that the needle tip does not lie within a blood vessel lumen. It is unnecessary to secure the needle in any way as it will not be moved if reasonable care is employed.

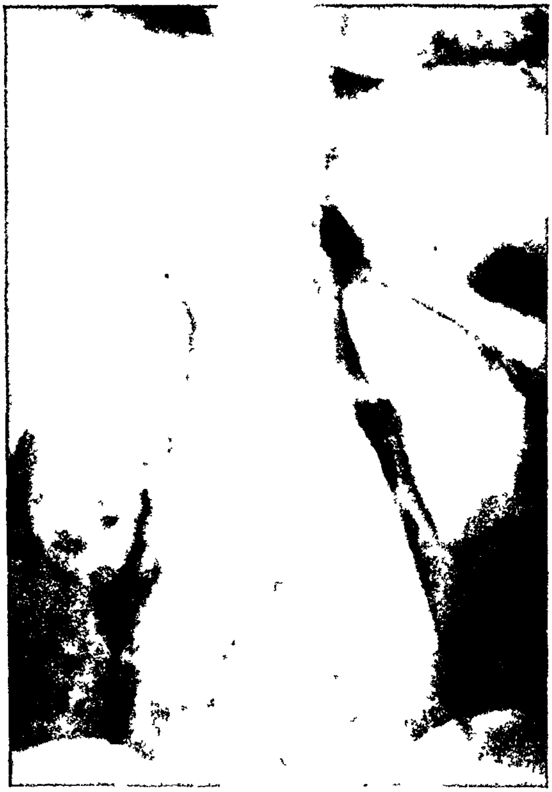

FIG. 2. Typical example of normal retrorectal oxygen insufflation in conjunction with excretory urography (neo-iopax).

We use a standard pneumothorax gas measuring device filled with oxygen as the gas source. This is led to one limb of a specially designed three-way stopcock, obtained through the courtesy of Mr. Jack Stein of Popper and Sons Inc., New York. The other limbs are connected one to the needle and the other to a standard 50 cc lock syringe. Hose end lock connections and pressure tubing are used throughout to prevent the connections from coming apart and to prevent gas leaks. A short length of pressure tubing is placed between the injecting syringe and the needle to permit some degree of mobility during the injection (fig. 1). This eliminates the hazard of moving the needle while manipulating the syringe. Oxygen is drawn into the syringe and injected in 50 cc increments. We have found that considerable pressure is required for the first 100–200 cc, but that following this the tissue planes appear to open up and practically no resistance is felt to further gas injection. As a further precaution the rectal finger may remain in place to detect the ballooning effect as gas is discharged into the tissues.

Depending on the size of the patient, we administer 1250–1750 cc for adults, taking about five minutes to complete the injection After several hundred cubic centimeters have been introduced almost all patients experience mild, transitory abdominal cramps The patients are closely observed during the period of injection for any signs which could conceivably be interpreted as evidence of embolization

Following completion of the injection the needle is withdrawn and a small hiss of escaping gas is occasionally heard, but this is not significant If desired, a collodion dressing may be applied to the puncture site The patient is instructed to assume a sitting posture for five to ten minutes to permit distribution of the gas, and then a scout film is taken of the abdomen to check the effectiveness of the insufflation (fig 2) Since there is free anatomical communication between the retroperitoneum and the mediastinum, some degree of mediastinal emphysema will develop in all patients This can be demonstrated by a chest x ray or the clinical finding of crepitus in the tissues of the neck While harmless, emphysema extending into the orbits is annoying to the patient and indicates overinjection

SUMMARY

A simple modification of the technique of retrorectal air insufflation has been presented The procedure is safe, easy, and incorporates all the advantages of the retrorectal route of insufflation

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THE USE OF A SHORT ACTING, MUSCLE RELAXANT DRUG (SUCCINYLCHOLINE CHLORIDE) IN DIAGNOSTIC UROGRAPHY: A PRELIMINARY REPORT

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Accuracy of diagnosis in Urology has been due chiefly to urography which has progressed rapidly in technique since its inception in 1906 by Von Lichtenberg and Voelcker. Clear cut renal and ureteral x-ray visualization is possible only when respiratory movements are stopped completely. The production of apnea during topical or spinal anesthesia is voluntary so it offers no problem but during general anesthesia it is more complex.

The use of thiopental (pentothal) or inhalation anesthesia for retrograde pyelograms is preferred frequently by patients as well as the attending urologist. The refinements of thiopental anesthesia have made it a safe, rapid, and inviting form of general anesthesia for urography if control of respiratory movement during the exposure of x-ray films can be obtained. Diaphragmatic movement, even if restricted, is often sufficient to blur pyelograms, though pressure is maintained on the abdominal wall by constricting bands or devices.

Three methods generally used for inducing apnea in the anesthetized patient are: large quantities of thiopental given rapidly, curarizing amounts of d-tubocurarine or induced hyperventilation with resultant apnea. Such procedures are not without some element of risk and frequently result in a deeply curarized or anesthetized patient at the conclusion of the procedure. An interesting complication is seen in figure 1 which shows the unexpected distention of the stomach and duodenum inadvertently produced while inducing apnea by the artificial hyperventilation method.

Anectine* (succinylcholine chloride) is diacetylcholine chloride, an "ultra-short-acting" muscle relaxant that has been found to be a safe and dependable drug for the production of apnea during general anesthesia. The rapid onset (20 to 40 seconds) of muscular relaxation and apnea following intravenous administration, coupled with brief duration of action (3 to 4 minutes) and the complete recovery without side effects, have made anectine invaluable to the anesthesiologist. Recognition of the value anectine may have in pyelography has prompted us to report a preliminary series of 25 pyelograms in which thiopental and nitrous oxide anesthesia was used for cystoscopy-retrograde pyelography. Apnea was produced by intravenous injection of anectine in dosages ranging from 10 to 30 mg. (0.5–1.5 cc) following insertion of ureteral catheters and instillation of 20 per cent iodopyracet (diodrast). Radiograms are made and when necessary respiration is assisted, using oxygen by means of the face mask and manual compression of the breathing bag until spontaneous respiration is re-

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* The anectine used in this study was supplied by courtesy of Burroughs, Wellcome & Co. (U. S. A.) Inc.

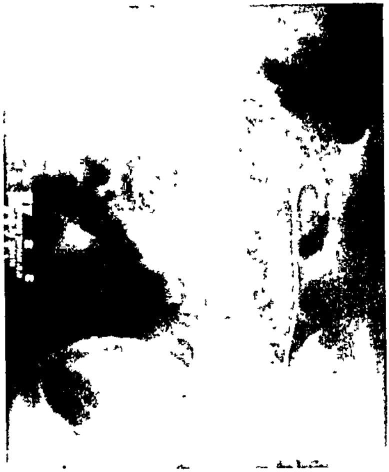

FIG. 1

sumed. Repeated injections are made as required for subsequent exposures The dangers of cumulative overdosages are not frequently encountered due to the rapid hydrolysis of the drug.

To demonstrate graphically and study more thoroughly the period of apnea and the sequences of events following anectine administration, we have employed spirography for thirteen of the above pyelograms. Figure 2 illustrates the adequate period of apnea for x-ray exposure that followed the injection of 20 mg. of anectine. We found periods of apnea 30 to 160 seconds in duration with an average of 78 seconds. Upon comparing critically the x-rays made by this method

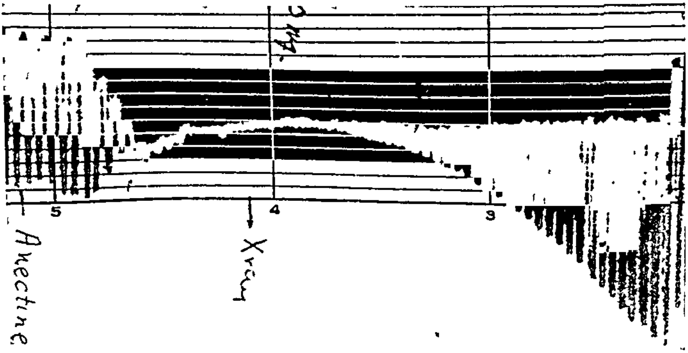

FIG. 2

and those taken when the patient is awake and able to co-operate by breath holding no significant difference can be detected.

A method of controlled respiration during general anesthesia to make satisfactory urography possible has been presented. Thirteen patients have been studied carefully by spirometric tracings and the same number of cases have been done by this method without spirometry; in no instances did any untoward incidence occur. It should be emphasized that equipment for positive pressure oxygenation and emergency intubation should be immediately available and that the anesthesiologist should be thoroughly familiar with such techniques whenever this drug is used.

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INSULATING SHEETS DURING TRANSURETHRAL RESECTION

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It is with some hesitancy that I present a simple gadget for the prevention of meatal burns during transurethral resections, for I am unfamiliar with general statistics of such complications.

Presumably in routine resections with equipment in good working order, burns of the urethral meatus should not occur. But, on several occasions, following transurethral resection of the prostate gland, an electrical burn occurred at the urethral meatus associated with desquamation and edema, and later as a soft stricture readily effaced after a few weeks. As soon as the burn was recognized, a check of the apparatus gave no clues. In each case the patient had an extremely long penile urethra, requiring pressure of the flange against the meatus.

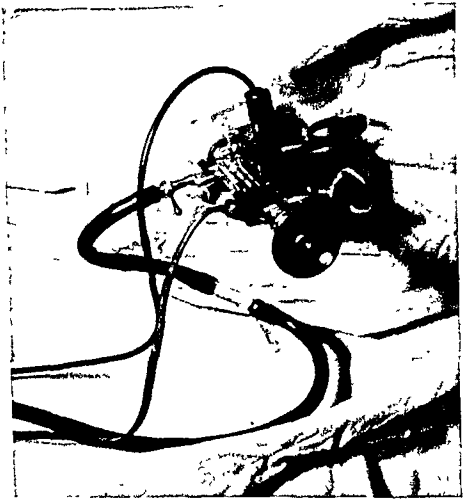

Fig. 1. Polyvinyl insulating sheet approximately 25 by 25 cm. Fenestra provided to admit No. 28 resectoscope sheath.

It was assumed that additional insulation may prevent this complication, and therefore a polyvinyl insulating sheet was devised (fig. 1). Since using this sheet no burns have been encountered. The problem was taken to Mr. F. J. Wallace, president of American Cystoscope Makers, Inc., and the polyvinyl material checked. We quote from Mr. Wallace:

Presented before the Chicago Urological Society, December 10, 1953.

"We have checked the material and find that it has a dielectric strength of 375 volts per mil, a power factor of .08 to .15 at 60 cycles, and a power factor of .04 to .14 at 10^6 cycles. Tests made with a circular electrode in contact with the material on an indifferent plate indicate that on 2 minutes exposure to 5000 volts at 60 cycles no puncture takes place. On the same test using vacuum tube high frequency current, a puncture occurs at 45 seconds, and a similar test using spark gap current results in a puncture at 15 seconds.

"The polyvinyl sheeting is a good electrical insulating material and should provide additional protection to a patient. The amount of radioactive frequency energy which passes through the metal shoulder of the bakelite sheath is extremely small, provided that the resectoscope is in proper working condition. This leakage current represents ground due to body capacity. If the patient is thoroughly grounded by the indifferent plate and if the instrument is held firmly in the hands of the operator, such small amounts of leakage current ground to the body, and should not produce any burn. The insulating sheet, as stated previously, will provide an additional measure of protection, and we will be glad to supply these sheets in small packets, and if you desire we will call them 'Fillis Insulating Sheets'."

It is hoped that this simple device may prevent the occasional meatal burn. It also serves a function in that the sheet will properly drape the glans, thus adding a little nicety that may be appreciated by the female personnel of cystoscopic departments. Its sterilization is carried out comparable to ureteral catheter sterilization.

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A WORKABLE SELF RETAINING RETRACTOR FOR RETROPUBIC PROSTATECTOMY

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In the 10 years since Millin's presentation the retropubic approach to the prostate has gained steadily in popularity. This approach, which is technically pleasing, has proven to be remarkably free of postoperative complications and the late results have been most gratifying. However, it shares with the perineal approach the disadvantages of requiring, at times, rather difficult exposure which usually necessitates four helping hands. After trying several types of self retaining retractors, some designed especially for the retropubic approach, we have in the past returned to a combination of two small Deaver retractors applied to the lateral fossae and a malleable spatula retractor for the bladder and peritoneum in the midline. This combination has proven most satisfactory but, of course, requires three hands. Recently we have devised a combination of these three instruments in a single self retaining retractor which has the necessary flexible adjustments to retain adjacent tissues for adequate exposure.

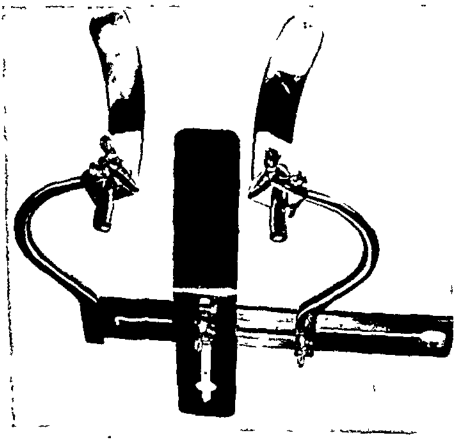

FIG. 1. Curve of lateral blades is demonstrated. They are adjustable to any desired direction and to necessary depth.

The salient features are: 1) lateral blades which utilize the approximate curve of a Deaver retractor and which are adjustable laterally at *every* angle and for depth of the wound; 2) a *completely* adjustable, malleable median blade for retraction of the bladder and peritoneum; 3) a frame of simple design and of size

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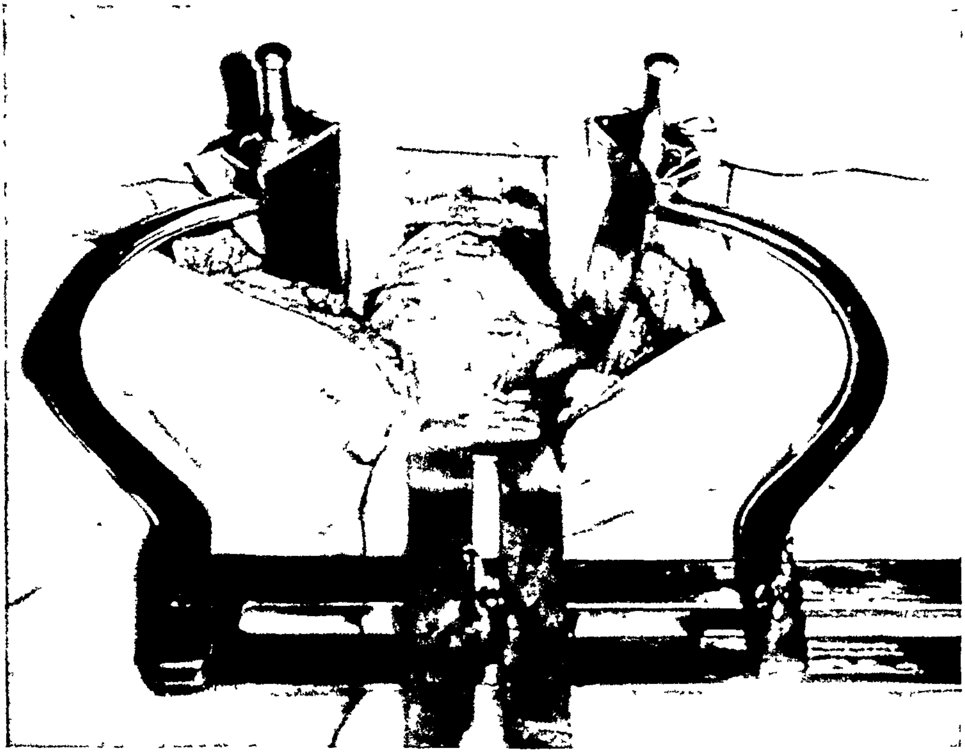

FIG. 2. Retractor in place showing anterior prostatic capsule with shorter marker directly over apex of prostate and longer marker over vesical neck. Note angle and depth of adjustable lateral blades necessary in this case for satisfactory exposure.

adequate to allow easy enucleation of the prostatic adenomas without removal of the retractor (fig. 1).

In use we have found it better to insert the lateral blades separately using protective sponges under the blades. The instrument gives good retraction of both the recti and prevesical fat and with the median malleable blade depressing the bladder, exposure of the prostate has been very satisfactory. In figure 2 the retractor is seen in place with a short marker placed directly over the apex of the prostate and a long marker just above the vesical neck. Note that the angle and depth of the lateral blades are easily adjustable for the variation in anatomy encountered in every case.

SUMMARY

A new self retaining retractor for retropubic prostatectomy is presented. The design incorporates the flexible adjustments necessary for use with varying anatomical configuration of the male pelvis.

This retractor was made through the kindness of Mr. Frederick J. Wallace of American Cystoscope Makers, Inc.

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Mid Atlantic—Haddon Hall, Atlantic City, April 13-16, 1955
North Central—Chicago, Ill , September 28-October 1, 1955
Northeastern—Lake Placid Club, N Y , September 22-24, 1955
South Central—San Antonio, Texas, October 17-19, 1955
Southeastern—Hotel Jung, New Orleans, La , March 21-23, 1955
Western—Hotel del Coronado, Coronado, Calif , January 24-27, 1955

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